1

FOOD & DRUG ADMINISTRATION (FDA)

CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)

PULMONARY-ALLERGY DRUGS

ADVISORY COMMITTEE (PADAC)

Mannitol Inhalation Powder

(Bronchitol)

NDA 202049

Wednesday, January 30, 2013

The Great Room

White Oak Conference Center

White Oak Campus, Building 31

10903 New Hampshire Avenue

Silver Spring, MD 20993

Reported by: Natalia Thomas

Capital Reporting Company

1   Meeting Roster

2   DESIGNATED FEDERAL OFFICER (Non-Voting)

3

4 Cindy Hong, PharmD

5 Division of Advisory Committee and Consultant

6 Management

7 Office of Executive Programs, CDER, FDA

8

9   PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE MEMBERS

10   (Voting)

11

12 Kathryn Blake, PhD

13 Senior Research Scientist

14 Nemours Children's Clinic

15 Jacksonville, Florida

16

17 Paul A. Greenberger, MD

18 Professor of Medicine, Department of Medicine

19 Division of Allergy-Immunology

20 Northwestern University Feinberg School of Medicine

21 Chicago, Illinois

22

 1   Meeting Roster

 2   (continued)

 3   PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE MEMBERS

 4   (Voting)(cont.)

 5

 6 David B. Jacoby, MD

 7 (Chairperson)

 8 Professor of Medicine

 9 Oregon Health and Science University

10 Division of Pulmonary and Critical Care Medicine

11 Portland, Oregon

12

13 Rodney Mullins

14 (Consumer Representative)

15 National Director, Public Health Consultants

16 and Advocates

17 Duluth, Georgia

18

19

20

21

22

1   Meeting Roster

2   (continued)

3   PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE MEMBERS

4   (Voting)(cont.)

5

6 Kelly Dean Stone, MD, PhD

7 Director, Allergy and Immunology Clinical Fellowship

8 Program

9 National Institutes of Allergy and Infectious Diseases

10 Bethesda, Maryland

11

12 Peter B. Terry, MD

13 Professor of Medicine

14 Division of Pulmonary and Critical Care Medicine

15 Johns Hopkins University School of Medicine

16 Baltimore, Maryland

17

18

19

20

21

22

```
 1                    Meeting Roster

 2                      (continued)

 3    PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE MEMBERS

 4                      (Non-Voting)

 5

 6  Howard M. Druce, MD

 7  (Industry Representative)

 8  Clinical Professor of Medicine

 9  Division of Allergy & Immunology

10  UMDNJ - University of Medicine and Dentistry

11  of New Jersey

12  New Jersey Medical School, Newark, New Jersey

13  Allergy and Immunology, Ear, Nose & Throat Care PC &

14  Allergy

15  Somerville, New Jersey

16

17

18

19

20

21

22
```

1   Meeting Roster

2   (continued)

3   TEMPORARY MEMBERS (Voting)

4

5   Robert G. Castile, MD, MS

6   Pediatric Pulmonologist

7   Nationwide Children's Hospital

8   Professor of Pediatrics

9   Ohio State University College of Medicine and

10 Public Health

11 Columbus, Ohio

12

13 Mary Cataletto, MD, FAAP, FCCP

14 Division of Pediatric Pulmonology

15 Winthrop University Hospital

16 Mineola, NY

17 Professor of Clinical Pediatrics

18 SUNY at Stony Brook

19 Stony Brook, New York

20

21

22

1   Meeting Roster

2   (continued)

3   TEMPORARY MEMBERS (Voting)(cont.)

4

5 John E. Connett, PhD

6 Professor

7 Division of Biostatistics

8 School of Public Health

9 University of Minnesota

10 Minneapolis, Minnesota

11

12 Michelle S. Harkins, MD, FCCP

13 Associate Professor of Medicine

14 Department of Internal Medicine, Pulmonary

15 and Critical Care Division

16 University of New Mexico

17 Albuquerque, New Mexico

18

19

20

21

22

1   Meeting Roster

2   (continued)

3   TEMPORARY MEMBERS (Voting)(cont.)

4

5 Amy H. Herring, ScD

6 Professor

7 Department of Biostatistics

8 Gillings School of Public Health

9 University of North Carolina at Chapel Hill

10 Chapel Hill, North Carolina

11

12 Richard B. Parad, MD, MPH

13 Associate Professor of Pediatrics

14 Harvard Medical School

15 Neonatologist

16 Department of Newborn Medicine

17 Brigham and Women's Hospital

18 Division of Respiratory Diseases

19 Boston Children's Hospital

20 Boston, Massachusetts

21

22

```
 1                    Meeting Roster

 2                     (continued)

 3          TEMPORARY MEMBERS (Voting)(cont.)

 4

 5  James M. Tracy, DO

 6  Assistance Clinical Professor of Internal Medicine

 7  Creighton University School of Medicine

 8  Managing Partner

 9  Allergy Asthma & Immunology Associates, P.C.

10  Omaha, Nebraska

11

12  Jeffrey S. Wagener, MD

13  Professor of Pediatrics

14  University of Colorado Medical School

15  Aurora, Colorado

16

17  TEMPORARY MEMBERS (Non-Voting)

18

19  Charles Hawkins

20  (Patient Representative)

21  Baltimore, Maryland

22
```

1   Meeting Roster

2   (continued)

3   FDA MEMBERS (Non-Voting)

4

5 Badrul Chowdhury, MD, PhD

6 Director

7 Division of Pulmonary, Allergy, and

8 Rheumatology Products (DPARP)

9 Office of Drug Evaluation II (ODE-II)

10 Office of New Drugs (OND), CDER, FDA

11

12 Anthony Durmowicz, MD

13 Clinical Team Leader

14 DPARP, ODE-II, OND, CDER

15

16 Kimberly Witzmann, MD

17 Clinical Reviewer

18 DPARP, ODE-II, OND, CDER

19

20

21

22

1   Meeting Roster

2   (continued)

3   FDA MEMBERS (Non-Voting)(cont.)

4

5 Thomas Permutt, PhD

6 Director

7 Division of Biostatistics II (DB-II)

8 Office of Biostatistics (OB)

9 Office of Translational Sciences (OTS), CDER, FDA

10

11 Feng Zhou, MS

12 Statistical Reviewer

13 DB-II, OB, OTS, CDER, FDA

14

15

16

17

18

19

20

21

22

1   TABLE OF CONTENTS

2   (continued)

3 AGENDA ITEM   PAGE

4

5 FDA PRESENTATIONS(cont.)

6

22

1   TABLE OF CONTENTS

2   (continued)

3 AGENDA ITEM   PAGE

4

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

1   P R O C E E D I N G S

2   Call to Order and Introduction of Committee Members

3   DR. JACOBY: If everyone could please take

4 their seats, we can get started. I would like to

5 remind everyone present please silence your cell

6 phones, as well as Blackberries and other devices, if

7 you haven't already done so.

8   I would also like to identify the FDA press

9 contact for this meeting, Ms. Morgan Liscinsky. Ms.

10 Liscinsky, are you -- thank you.

11   My name is David Jacoby. I am the Chair for

12 the Pulmonary-Allergy Drugs Advisory Committee. I will

13 now call this meeting of the Pulmonary-Allergy Drugs

14 Advisory Committee to order.

15   We will start by going around the table and

16 introducing ourselves. Let's start on the right.

17   DR. DRUCE: Good morning. My name is Howard

18 Druce. I'm a clinical professor of medicine at the New

19 Jersey Medical School in Newark, and I'm in private

20 practice in allergy and immunology in Somerville, New

21 Jersey.

22   DR. CATALETTO: My name is Mary Cataletto.

1 I'm a professor of clinical pediatrics at SUNY Stony

2 Brook, and I practice clinical pediatric pulmonology.

3   DR. CASTILE: I'm Bob Castile. I practice

4 pediatric pulmonology at Nationwide Children's Hospital

5 in Columbus, Ohio.

6   DR. PARAD: My name is Richard Parad. I am a

7 neonatologist and pediatric pulmonologist at Boston

8 Children's Hospital, and Brigham and Women's Hospital,

9 Harvard Medical School.

10   DR. WAGENER: I'm Jeff Wagener. I am a

11 professor of pediatrics from the University of

12 Colorado, and recently retired.

13   DR. HARKINS: Michelle Harkins, associate

14 professor of medicine, University of Mexico, adult

15 pulmonary and critical care.

16   DR. CONNETT: I'm John Connett. I am

17 professor of biostatistics at the University of

18 Minnesota.

19   DR. STONE: Kelly Stone. I'm a pediatrician

20 and allergist/immunologist in the Laboratory of

21 Allergic Diseases, NIAID.

22   DR. BLAKE: I'm Kathryn Blake, Senior

1 Research Scientist in the Center for Pharmacogenomics

2 and Translational Research at Nemours Children's Clinic

3 in Jacksonville, Florida.

4   DR. JACOBY: David Jacoby. I'm chief of

5 pulmonary and critical care at Oregon Health and

6 Science University in Portland.

7   DR. HONG: Hi. I'm Cindy Hong, the

8 designated federal officer for the Pulmonary-Allergy

9 Drugs Advisory Committee.

10   DR. TERRY: Peter Terry, professor of

11 medicine, pulmonary and critical care, Johns Hopkins.

12   DR. GREENBERGER: Paul Greenberger, professor

13 of medicine, Division of Allergy-Immunology at

14 Northwestern University, Feinberg School of Medicine.

15   MR. MULLINS: Rodney Mullins from Atlanta,

16 Georgia, chair of the Health Advisory Coalition and

17 director of National Public Health Advocates.

18   DR. TRACY: Jim Tracy, associate professor of

19 medicine, Creighton University, Division of Allergy and

20 Immunology, and in private practice in Omaha.

21   DR. HERRING: Amy Herring, professor of

22 biostatistics, the University of North Carolina at

1 Chapel Hill.

2   MR. HAWKINS: Charles Hawkins. I'm a patient

3 with cystic fibrosis here representing that group of

4 people.

5   MS. ZHOU: Feng Zhou, statistical reviewer,

6 FDA.

7   DR. PERMUTT: Tom Permutt, director, Division

8 of Biometrics II.

9   DR. WITZMANN: Kimberly Witzmann, clinical

10 reviewer for FDA, and I'm a pediatric pulmonologist by

11 training.

12   DR. DURMOWICZ: I'm Tony Durmowicz. I'm a

13 pediatric pulmonary and critical care physician, here

14 in the pulmonary allergy/rheumatology group.

15   DR. CHOWDHURY: I'm Badrul Chowdhury. I'm

16 the division director, Division of Pulmonary, Allergy,

17 and Rheumatology Products at the FDA.

18   DR. JACOBY: Thank you. Thank you, everyone,

19 for being here.

20   For topics such as those being discussed at

21 today's meeting, there are often a variety of opinions,

22 some of which are quite strongly held. Our goal is

1 that today's meeting will be a fair and open forum for

2 discussion of these issues, and that individuals can

3 express their views without interruption.

4   Thus, as a gentle reminder, individuals will

5 be allowed to speak into the record only if recognized

6 by the chair. We look forward to a productive meeting.

7   In the spirit of the Federal Advisory

8 Committee Act and the Government in the Sunshine Act,

9 we ask that the Advisory Committee members take care

10 that their conversations about the topic at hand take

11 place in the open forum of the meeting.

12   We are aware that members of the media are

13 anxious to speak with FDA about these proceedings.

14 However, FDA will refrain from discussing the details

15 of this meeting with the media until its conclusion.

16   Also, the Committee is reminded to please

17 refrain from discussing the meeting topic during breaks

18 or lunch.

19   Thank you. Conflict of Interest Statement

20   DR. HONG: The Food and Drug Administration

21 is convening today's meeting of the Pulmonary-Allergy

22 Drugs Advisory Committee under the authority of the

 1 Federal Advisory Committee Act of 1972. With the

 2 exception of the industry representative, all members

 3 and temporary members of the Committee are special

 4 government employees or regular federal employees from

 5 other agencies and are subject to federal conflict of

 6 interest laws and regulations.

 7   The following information on the status of

 8 those committees' compliance with federal ethics and

 9 conflict of interest laws covered by, but not limited

10 to, those found at 18 USC Section 208 is being provided

11 to participants in today's meeting and to the public.

12   FDA has determined that members and temporary

13 voting members of this Committee are in compliance with

14 federal ethics and conflict of interest laws. Under 18

15 U.S.C Section 208, Congress has authorized FDA to grant

16 waivers to special government employees and regular

17 federal employees who have potential financial

18 conflicts where it is determined that the agency's need

19 for a particular individual's service outweighs his or

20 her potential financial conflict of interest.

21   Related to the discussions of today's

22 meeting, members and temporary members of this

1 Committee have been screened for potential financial

2 conflicts of interest of their own as well as those

3 imputed to them, including those of their spouses or

4 minor children, and, for purposes of 18 USC Section

5 208, their employers.

6   These interests may include investments,

7 consulting, expert witness testimony, contracts,

8 grants, CREDAs, teaching, speaking, writing, patents

9 and royalties, and primary employment.

10   Today's agenda involves discussion of New

11 Drug Application 2020494, mannitol inhalation powder,

12 proposed trade name bronchitol for oral inhalation,

13 sponsored by Pharmaxis for the proposed indication of

14 management of cystic fibrosis in patients age six years

15 and older to improve pulmonary function.

16   This is a particulate matters meeting during

17 which specific matters related to Pharmaxis' mannitol

18 will be discussed. Based on the agenda and all

19 financial interests reported by the Committee members

20 and temporary matters, no conflict of interest waivers

21 have been issued in connection with this session.

22   To ensure transparency, we encourage all

1 standing Committee members and temporary voting members

2 to disclose any public statements that they have made

3 concerning the product at issue.

4   With respect to FDA's invited industry

5 representative, we would like to disclose that Dr.

6 Howard Druce is participating in this meeting as a non-

7 voting industry representative, acting on behalf of

8 regulated industry. Dr. Druce's role at this meeting

9 is to represent industry in general and not any

10 particular company. Dr. Druce is an independent

11 pharmaceutical industry consultant.

12   We would like to remind members and temporary

13 voting members that if the discussions involve any

14 other products or firms not already on the agenda for

15 which an FDA participant has a personal or imputed

16 financial interest, the participants need to exclude

17 themselves from such involvement, and their exclusion

18 will be noted for the record.

19   FDA encourages all other participants to

20 advise the Committee of any financial relationships

21 that they may have with the firm at issue.

22   Thank you.

1   DR. JACOBY: We will now proceed with

2 the FDA opening remarks from Dr. Anthony Durmowicz. I

3 would like to remind public observers of this meeting

4 that, while this meeting is open for public

5 observation, public attendees may not participate

6 except at the specific request of the panel. Opening

7 Remarks

8   DR. DURMOWICZ: Good morning, and I would

9 like to welcome everyone here to White Oak, and thank

10 you for your participation in the Pulmonary-Allergy

11 Drugs Advisory Committee meeting today.

12   The objective of today's discussion will be

13 to look at the efficacy and safety data for the NDA

14 from Pharmaxis Limited for inhaled mannitol to treat

15 patients with cystic fibrosis to improve pulmonary

16 function.

17   I think you are going to hear some detailed

18 presentations from both the applicant as well as the

19 FDA today, so I will be very brief in outlining the

20 clinical program for inhaled mannitol and outline some

21 key issues that you will be asked to deliberate on

22 later.

 1   As many or most already know, mannitol is a

 2 commonly used and recognized sugar alcohol. It is used

 3 as an osmotic diuretic in medicine. It is generally

 4 recognized as safe by the enteral route.

 5   For the inhalation indication that is being

 6 sought today, the indication is for management of

 7 cystic fibrosis in patients six years and older to

 8 improve pulmonary function. The proposed dose is 400

 9 milligrams taken as 10 capsules by inhalation twice

10 daily.

11   You should also note that a closely related

12 product of inhaled mannitol called aridol is approved

13 by the FDA as a test kit similar to methacholine to

14 assess airway hyperresponsiveness. And as such, in

15 some patients there can be a side effect of severe

16 bronchial constriction.

17   Also of note is that there are other mucus

18 clearance agents that are used for cystic fibrosis.

19 One inhaled hypertonic saline is commonly used and has

20 become a standard of care for many cystic fibrosis

21 patients in the United States, although it is not FDA

22 approved for use. Another mucus clearance or mucolytic

1 agent is DNase, also known as pulmozyme.

2   I won't dwell too long on what cystic

3 fibrosis is, as many of the Committee members are well

4 aware. It is, however, an autosomal recessive genetic

5 disorder caused by mutations in the cystic fibrosis

6 transmembrane regulator gene. Loss of function in the

7 CFTR protein leads to the multi-organ abnormalities

8 that are associated with cystic fibrosis. These

9 include airway obstruction with subsequent pulmonary

10 infection, pancreatic insufficiency and other GI

11 abnormalities, and reproductive problems.

12   There are approximately 30,000 patients in

13 the U.S. with cystic fibrosis. And despite significant

14 advances, CF remains a serious disease which is

15 ultimately fatal to many people.

16   With the exception of the recently approved

17 drug ivacaftor, which is approved in only a very small

18 subpopulation of cystic fibrosis patients, current

19 therapies treat only symptoms and complications of the

20 disease.

21   The clinical program for inhaled mannitol for

22 cystic fibrosis was fairly small, as would be expected

1 for an orphan disease. Study 202 provided the main

2 evidence for dose selection. It was an open-label,

3 crossover study with two-week treatment periods and

4 approximately 48 patients. The primary endpoint was

5 percent change in FEV1.

6   This study formed the basis for selection of

7 the 400 milligram, twice daily proposed dose, as well

8 as the selection of the 50 milligram dose as a control

9 based on lack of effect of a 40 milligram dose in that

10 trial.

11   There were two Phase III trials, Studies 301

12 and 302. Both were very similar in design. Both were

13 double-blinded, controlled, parallel group studies of

14 26- week duration, double-blinded periods. Both had

15 approximately 300 patients. The primary endpoint was

16 absolute change in FEV1 across the 26-week treatment

17 period compared to placebo.

18   It is notable that these studies were not

19 conducted concurrently. Study 301 was conducted first,

20 followed by Study 302.

21   I would like to now go through some of the

22 issues with the program that you will be asked to

1 deliberate upon later today.

2   Far and away the most problematic issue was

3 that of missing data. There was a high degree of

4 differential dropout, more so in the treatment group

5 than in the control group. This is especially true for

6 the first study, Study 301. As such, sensitivity

7 analyses were required in order to be able to assess

8 the interpretability of the study results.

9   Also, how much of a treatment effect is also

10 somewhat questionable, likely because of the

11 differential dropout and multiple sensitivity analyses.

12 At the end of the day, however, it appears that there

13 is a single study which has demonstrated efficacy and a

14 second study which is statistically negative or

15 equivocal.

16   Sensitivity analyses that you will see

17 presented suggest that a treatment effect is in a range

18 of a certain set of values, approximately 50 to 80

19 milliliters. And from a clinical perspective, one of

20 the issues is, is that clinically significant in this

21 population?

22   As I mentioned previously, there is a known

1 safety issue with the bronchial provocation agent. In

2 the clinical trials, there is also increased amounts of

3 hemoptysis in treatment patients. Pediatrics is also a

4 topic for discussion.

5   So at the end of the day, we have three main

6 discussion issues. One is the efficacy determination,

7 and that boils down to, is there substantial evidence

8 of efficacy as we define it? Taking into consideration

9 the impact of the missing data and differential dropout

10 in the sensitivity analysis suggesting a range of

11 effect on FEV1, rather than being able to pinpoint it a

12 little bit more accurately, as well as the clinical

13 relevance of the range of treatment effects that you'll

14 see.

15   Safety is also to be discussed, again, as I

16 mentioned, with the potential safety concerns, most

17 notably hemoptysis and respiratory adverse events. And

18 with regard to pediatrics, there is -- the issue is, is

19 there sufficient data to suggest there is evidence of

20 efficacy and acceptable safety in that population of

21 children six to 17 years of age?

22   With that, thank you for your attention, and

1 I will turn the podium back over to Dr. Jacoby.

2   Thank you.

3   DR. JACOBY: Thank you. We will now proceed

4 with the sponsor presentations. Both the Food and Drug

5 Administration and the public believe in a transparent

6 process for information-gathering and decision-making.

7 To ensure such transparency at Advisory Committee

8 meetings, FDA believes it is important to understand

9 the context of an individual's presentation. For this

10 reason, FDA encourages all participants, including

11 sponsor's non-employee presenters, to advise the

12 Committee of any financial relationships that they may

13 have with the firm at issue, such as consulting fees,

14 travel expenses, honoraria, and interest in the

15 sponsor, including equity interests and those based on

16 the outcome of the meeting.

17   Likewise, FDA encourages you at the beginning

18 of your presentation to advise the Committee if you do

19 not have any such financial relationships. If you

20 choose not to address this issue of financial

21 relationships at the beginning of your presentation, it

22 will not preclude you from speaking. Sponsor

1 Presentations Introduction

2   DR. DUNDORE: Good morning. I am Ron

3 Dundore, vice president of U.S. Regulatory Affairs for

4 Pharmaxis. We appreciate the opportunity to review the

5 NDA for the use of dry powder mannitol, DPM, in

6 patients with cystic fibrosis with this Advisory

7 Committee.

8   The proposed indication for DPM is the

9 management of cystic fibrosis in patients age six years

10 and older to improve pulmonary function. Patients with

11 FEV1 less than 30 percent predicted, and patients with

12 a history of recent significant hemoptysis, were

13 excluded from the Phase III trials, and, accordingly,

14 we have excluded them from the proposed label.

15   After an extensive review of the data

16 obtained in our clinical studies, we also propose to

17 exclude patients with FEV1 less than 40 percent because

18 of uncertain benefit risk in this subpopulation.

19   DPM is a novel proprietary formulation of

20 mannitol for inhalation. Mannitol is generally

21 recognized as safe or GRAS by the FDA when used as a

22 food additive, allowing exposure of 20 grams per day,

1 significantly above any medicinal use. The dose of DPM

2 is 400 milligrams BID. It is currently approved for

3 the treatment of cystic fibrosis in Europe and

4 Australia.

5   Pharmaxis currently markets another inhaled

6 mannitol preparation in the U.S., proprietary name

7 aridol. Aridol is used to test for bronchial

8 hyperresponsiveness. With the exception of dose, the

9 preparation of mannitol in aridol is exactly the same

10 as in DPM.

11   With aridol, the total dose of inhaled

12 mannitol is 635 milligrams. Within the lung, mannitol

13 may act as an osmotic agent to promote airway

14 clearance. Non- clinical studies have shown that

15 mannitol induces an influx of water into the airway

16 lumen and increases the airway surface liquid.

17 Mannitol facilitates the transportability of mucus and

18 increases the ciliary beat frequency of human ciliated

19 bronchial endothelial cells.

20   Clinical studies have shown that inhaled

21 mannitol improves mucociliary clearance in healthy

22 subjects and in patients with cystic fibrosis, as well

1 as asthma and bronchiectasis. Therefore, inhaled

2 mannitol hydrates the surface of the lung, decreases

3 the viscosity of the mucus, and allows the patient to

4 more easily expel the thick viscous mucus that is a

5 symptom of cystic fibrosis. The expulsion of the mucus

6 improves airway clearance and lung function.

7   DPM is engineered to provide optimal

8 deposition of mannitol in the lung. A solution of

9 mannitol is spray-dried to produce consistent smears of

10 three micrometers in diameter, ensuring optimized

11 delivery to the lung. The dry powder mannitol is

12 placed in capsules containing 40 milligrams. The total

13 dose of 400 milligrams is administered by a breath-

14 actuated dry powder inhaler.

15   Here is how the inhaler works. The process

16 starts by removing the cap. To open the inhaler you

17 simply twist the top and place a capsule in the

18 chamber. After closing the inhaler, you press the

19 buttons on the side to puncture the capsule and then

20 release. Finally, you place the inhaler in your mouth,

21 tilt your head back, and take a deep breath, holding it

22 for five seconds.

1   You then breathe out, away from the inhaler.

2   This process is then repeated for the remaining

3   capsules. The entire 400 milligram administration time

4   is approximately five minutes. The inhaler is portable

5   and disposable, requiring no routine cleaning.

6   Importantly, DPM is designed for patient convenience.

7   With this background in mind, I would like to

8   review the outline for our presentation. Dr. Felix

9   Ratjen will discuss the unmet medical need in the

10 treatment of cystic fibrosis. Dr. Howard Fox will

11 present the Phase III studies that demonstrate the

12 efficacy of DPM and will describe the statistical

13 methods used to assess efficacy.

14   Dr. Brett Charlton will discuss the safety of

15 DPM, and Dr. Patrick Flume will discuss the

16 risk/benefit of DPM and provide a clinical perspective.

17   In addition, we have other experts with us

18 today to help address your questions. Dr. Bilton has

19 used DPM to treat a number of her CF patients and can

20 address your questions about patient tolerability and

21 compliance and clinical utility. The experts have been

22 compensated for their time.

1   I would now like to turn the presentation

2 over to Dr. Ratjen. Unmet Medical Need

3   DR. RATJEN: Thank you. I would like to

4 disclose that I act as a consultant for Pharmaxis and

5 have been reimbursed for activities like this one.

6   So I appreciate the opportunity to provide a

7 background on cystic fibrosis, since I have dedicated

8 much of my professional life to the study and treatment

9 of this debilitating disease. As you already have

10 heard and probably know, cystic fibrosis is an

11 autosomal recessive disease resulting from mutations in

12 CFTR.

13   Cystic fibrosis is one of the most common

14 genetically inherited diseases. In the United States,

15 it is considered an orphan disease affecting more than

16 30,000 patients, and about 1,000 new cases are

17 diagnosed each year, nowadays mostly by newborn

18 screening. And despite significant advances in

19 treatment, the estimated median life expectancy is

20 approximately 38 years in the U.S. today.

21   And these incremental improvements in life

22 expectancy have been the result of multiple modest

1 improvements in therapy. Still, the overall morbidity

2 and mortality of cystic fibrosis patients remains

3 unacceptably high.

4   Cystic fibrosis is a multi-organ disease, but

5 the lungs remain the most severely affected organ with

6 exacerbations and infections accounting for 75 percent

7 of hospitalizations, and 90 percent of deaths

8 associated with cystic fibrosis.

9   Lung disease is progressive in cystic

10 fibrosis patients, and lung function declines over

11 time, and this is measured by FEV1. As shown here on

12 the left side of the graph, in children with cystic

13 fibrosis nowadays most children have lung function in

14 the normal range.

15   So the goal of cystic fibrosis therapy is to

16 minimize and/or delay lung function decline over time.

17 And exacerbations and infections contribute to lung

18 function decline and increase in incidence as the

19 disease progresses. They have also been linked to

20 overall disease mortality. Therefore, lessening

21 exacerbation is an important goal of therapy.

22   Let's now examine the cystic fibrosis disease

1 pathophysiology. So mutation of CFTR causes a cascade

2 of consequences. CFTR dysfunction causes depletion of

3 airway surface liquid. This dehydration leads directly

4 to increased stickiness of airway mucus, and this

5 results in impaired mucociliary clearance, which is an

6 important defense mechanism to maintain normal lung

7 hygiene. And poor clearance causes mucus obstruction

8 and chronic airway obstruction.

9   Mucus retention then favors bacterial

10 colonization and persistence of infection, and

11 bacterial infection results in chronic inflammation,

12 which is an important cause of lung damage. And this

13 vicious cycle of infection and inflammation is

14 initiated by mucus retention, leading to degradation of

15 lung structure and function, and ultimately

16 contributing to the untimely death of our patients.

17   And this highlights the importance of airway

18 clearance as a mechanism to improve lung health in

19 cystic fibrosis.

20   So strategies for CF therapies have been

21 outlined in current guidelines. These include DNase,

22 bronchodilators, inhaled antibiotics, as well as

1 macrolides, which work lower in the cystic fibrosis

2 cascade, treating the symptoms of the disease. Our

3 desire is to find treatments that work higher in the

4 pathophysiological cascade, working directly on CFTR,

5 like ivacaftor.

6   Ivacaftor works to potentiate the CFTR

7 protein, so that rehydration of the airway and airway

8 clearance are improved. However, it has only been

9 proven effective for about four percent of the CF

10 patients that have one specific genotype. Thus, a

11 medical need exists for treatment that intervenes early

12 in the disease cascade to improve airway clearance.

13 Such a treatment should be available to all patients,

14 regardless of age or disease severity, to improve lung

15 function and reduce exacerbations.

16   So one of these possibilities is to improve

17 mucociliary clearance by hydrating the airway surface

18 liquid. There is currently no approved therapy that

19 addresses mucociliary clearance. Hypertonic saline,

20 while not approved, is recommended in the cystic

21 fibrosis guidelines. However, its tolerability varies

22 and nebulization is time-consuming; thus, the need for

1 new treatments such as mannitol that can be added to

2 current therapy to increase surface liquid, airway

3 surface liquid, and to improve mucociliary clearance in

4 a convenient fashion.

5   So while these products are recommended by

6 the CF guidelines, not every patient will be treated

7 with all available products. Due to the progressive

8 nature of the disease, we, as clinicians, try each

9 product in an effort to maintain lung function over

10 time.

11   So how do we arrive at the best therapy for

12 each patient? So the factors that lead to

13 individualized treatment are response, tolerability,

14 and acceptability by patients. Yet we also need to

15 consider the enormous treatment burden facing our CF

16 patients, and much of that treatment burden has to do

17 with the many challenges of nebulized therapy.

18   Some publications cite that patients perform

19 an average of seven therapies per day and spend almost

20 two hours each day with inhaled therapies like domase

21 alpha or antibiotics. Nebulizer therapy also limits

22 the mobility of patients, and ease of use and

 1 portability become important considerations.

 2   So, in addition, setup and cleaning of

 3 nebulizers is time-consuming, and only a third of

 4 patients actually follow recommended cleaning

 5 procedures. So nebulizers can actually become

 6 contaminated with bacteria, leading to a further risk

 7 of infection.

 8   So it is a challenge for many cystic fibrosis

 9 patients. They want to feel better by their treatment,

10 but it is so burdensome that they fail to fully comply.

11 So additional options are needed; however, only if

12 these treatments don't add burden to our already

13 burdened patients.

14   So we need options that can be added to

15 patients' current management, be it a child or an

16 adult, to improve lung health. And a key goal in

17 treating cystic fibrosis is to improve airway clearance

18 by enhancing mucociliary clearance.

19   When I am talking to my patients, I say

20 maintaining lung function over time is a good thing,

21 but improvements are even better. Thus, any sustained

22 incremental improvement in lung function is important

1 to both physicians and to our patients. Similarly, as

2 exacerbations drive lung function decline, any

3 reduction in exacerbations are equally important.

4 These actions help to slow the decline in lung function

5 and have been linked to relative improvements in

6 morbidity and mortality.

7   Finally, additional therapies should not add

8 significant burden of treatment. Even optimal

9 therapies don't work if the patients don't use them.

10 Simply put, poor adherence leads to impaired control of

11 the disease. Therefore, effective therapy that patients

12 willingly continue to take is desired by both patients

13 and their clinicians.

14   Thank you. I will now turn the presentation

15 over to Dr. Fox. Efficacy

16   DR. FOX: Thank you, Professor Ratjen. I'm

17 Howard Fox, chief medical officer at Pharmaxis. I'd

18 like to present data from the dry powder mannitol

19 program that is representative of the cystic fibrosis

20 population, including that of the United States.

21   The data is consistent with an effect derived

22 from improved airway clearance and supports why the

1 clinical benefits of DPM at the 400 milligram dose are

2 clinically meaningful. I will first provide a brief

3 overview of the clinical program, followed by a more

4 detailed description of the Phase III study designs,

5 and then I will present data from Study 301 followed by

6 302. And then, finally, I will share subgroup analyses

7 based on the pooled data.

8   Now, the challenging nature of studies in

9 this orphan disease means that the studies must be

10 interpreted based on the entirety of evidence rather

11 than FEV1 alone. I will also address two important

12 topics needing consideration.

13   Firstly, I will present the detailed review

14 of the sensitivity analyses showing why we can conclude

15 that there is a significant effect in CF-301 despite a

16 higher- than-expected withdrawal rate; secondly, why,

17 despite the primary endpoint narrowly missing

18 statistical significance in CF-302, it does show a

19 meaningful effect.

20   Now, DPM's program in cystic fibrosis is

21 comprised of five studies. In the Phase II program,

22 Study 201 compared 420 milligrams of mannitol twice

1 daily to placebo in a two-week crossover design. 202

2 was a dose ranging study, again crossover, comparing

3 doses between 40 and 400 milligrams twice daily. And

4 Study 203 compared open-label DPM to rhDNase and their

5 combination.

6   CF-301 and 302 formed the Phase III program,

7 which I will later describe in more detail and which

8 form the basis of the application.

9   Now, I should point out that the control in

10 the Phase III program was a 50 milligram dose of

11 mannitol.

12   Now, I will now provide you with the Phase II

13 results that support our proposed dosing. This figure

14 summarizes the dose ranging results from CF-202 with

15 change in FVC on the Y-axis and the four doses from 40

16 to 400 milligrams studied.

17   Now, this study supports the choice of the

18 400 milligram dose for DPM in the NDA. And although we

19 did not confirm that this was a maximally effective

20 dose, we considered that more than 10 capsules with one

21 dose may not be acceptable. The 40 milligram dose

22 suggests that the 50 milligram control dose used

1 subsequently in the Phase III studies is likely to have

2 been subtherapeutic.

3   Moving on then to the Phase III trials, which

4 formed one of the largest programs conducted in this

5 orphan designated disease, and that included 139

6 patients from 28 centers in the United States. The two

7 Phase III studies were of near identical design, both

8 being multi- center, double-blind, controlled, six-

9 month safety and efficacy studies that were randomized

10 in a three-to-two ratio.

11   Patients had confirmed diagnosis of cystic

12 fibrosis, were six years or older. The FEV1s were in

13 the 30 to 90 percent predicted range, 40 percent in the

14 case of 302. All standard approved therapy was

15 allowed, and regular therapy had to remain unchanged

16 throughout the studies.

17   Hypertonic saline was not allowed for reasons

18 of confounding data. Like hypertonic saline, mannitol

19 can provoke bronchial hyperactivity in people who are

20 sensitive. And, therefore, all study patients first

21 had to pass a mannitol tolerance test, or MTT.

22   Also, patients were routinely pre-dosed with

1 a bronchial dilator, such as albuterol, both prior to

2 testing and before study drug administration throughout

3 the study's duration. This schematic shows each study

4 starting with the screening visit, which included the

5 MTT, and randomization also took place at this point.

6   And then there was a two- to five-week period

7 before the start of study drug, the RTT comprised of

8 randomized patients who had received at least one dose

9 of study drug. From baseline, patients received either

10 400 milligrams of mannitol or 50 milligrams control, as

11 10 capsules twice daily, for the 26 weeks of the

12 double- blind phase, during which time patients were

13 reassessed, including by spirometry, at weeks 6, 14,

14 and 26.

15   And then, at the end of the 26 weeks,

16 patients could enter an open-label phase where they all

17 received 400 milligrams twice daily in addition to

18 their standard care.

19   So moving on to the results from the pivotal

20 study, CF-301, and I'll begin with endpoints. Here the

21 primary endpoint was change from baseline in FEV1 over

22 the 26-week, double-blind study period. FEV1 is a

1 widely accepted primary variable in CF studies, and its

2 decline is associated with both increased morbidity and

3 mortality

4 Clinically relevant secondary variables included other

5 lung function parameters such as forced vital capacity

6 and exacerbations. Now, these collected based on Fuchs

7 criteria, which included a requirement of intravenous

8 antibiotic use. And we also evaluated sputum weight.

9   Key endpoints were also evaluated by rhDNase

10 use subgroups, and there were also some post-hoc

11 analyses, but my slides here will indicate any not

12 planned prospectively.

13   The primary endpoint, FEV1, was analyzed by a

14 mixed model repeated measures, or MMRM, and that's

15 based upon change from baseline at the three visits

16 over 26 weeks. Now, the MMRM analysis does require at

17 least one followup measure for a patient to be

18 included. And, therefore, the ITT population could not

19 be used for this particular analysis.

20   Therefore, the primary analysis, as dictated

21 by this pre-specified model, is the full analysis set,

22 or FAS. The FDA, in their briefing book, referred to

1 the primary analysis population as the Pharmaxis MITT.

2 Where feasible, the ITT population, which is the same

3 as the FDA ITT, was used for other measures. The ITT

4 population was also used for the sensitivity analyses

5 of the primary endpoint.

6   Now, the intent to treat population comprised

7 295 patients, and the full analysis set totaled 272.

8 And I'd like to walk you through how we get to those

9 numbers.

10   So, firstly, 378 patients were screened. The

11 most common reason for not being randomized, in 27

12 patients of those screened, was due to a failed MTT to

13 the 400 milligram dose. And this represents 7.1

14 percent of those screened.

15   Twenty-nine of the 324 randomized patients

16 withdrew before receiving study drug, with only five

17 due to adverse events, leaving us with 295 patients

18 meeting the ITT definition.

19   Study 301 ITT contained 177 patients on DPM

20 and 118 on control. From the ITT, 18 of the DPM

21 patients and five on control withdrew before week six,

22 meaning that 159 patients on DPM and 113 on control

1 made up the full analysis set. Therefore, the full

2 analysis set used to calculate the primary endpoint is

3 based upon 92.2 percent of the ITT.

4   Now, between week six and the end of the

5 double- blind phase, a further 47 patients in the DPM

6 group and 27 in the control have withdrawn, leaving 112

7 completers in the DPM group and 86 in the control.

8 Now, the overall withdrawal rate was high, although it

9 was comparable to the 27 percent seen in a recent CF

10 study in tobramycin.

11   The most common reason for withdrawal was

12 withdrawal of consent, which was more common in the

13 control arm. And next was adverse event, which was

14 twice as common in the DPM arm.

15   The demographics now in CF-301 were balanced

16 between arms and reasonably representative of the CF

17 population over six years of age, and is on average of

18 moderate severity based on FEV1 percent predicted.

19   rhDNase and inhaled antibiotic use was

20 widespread, reflecting best standard of care.

21   Now, the primary endpoint result, using

22 methodology as set out in our statistical analysis

1 plan, supports the efficacy of DPM. The FEV1 change

2 from baseline is shown here in mLs on the Y-axis.

3 Study 301 successfully demonstrated a significant

4 improvement of 83 mLs compared to control over the

5 double-blind 26-week study period, with a P value of

6 less .001, remembering this is also over and above by

7 standard of care.

8   Now, the pivotal studies were designed to

9 evaluate the effect over the six months. However,

10 post- hoc we examined the FEV1 changes also at each

11 time point. And these support the maximum effect on

12 FEV1 change had already been reached by the first

13 followup visit at week six, and the data also supports

14 an improvement from baseline still being sustained up

15 to six months.

16   Now, as withdrawal was unbalanced between

17 groups, which may not have been random, we do recognize

18 the potential to bias the results. And it's important

19 that we consider the impact of unbalanced withdrawal on

20 our estimate of effect size. And, therefore, in the

21 next series of slides, I will go through in some detail

22 how we address this.

1   The primary model MMRM imputes for missing

2 data as shown with the dotted lines in this figure, and

3 assumes missing data are missing but random. However,

4 this may or may not be the case. And, therefore, the

5 possibility of bias can't be excluded. And this is

6 particularly true for any patients withdrawing in the

7 first six weeks of the study who did so before any

8 post- baseline FEV1 data was collected, to inform

9 whether they were improving or worsening when they

10 left.

11   And in fact, the greater number of patients

12 in the DPM arm withdrawing before week six compared to

13 control was the main driver of differential dropouts,

14 and this was mainly due to adverse events. These

15 patients are not part of the FAS.

16   Importantly, however, 92 percent of the ITT

17 population did contribute data to the primary analysis

18 based on the FAS, limiting the degree of likely bias.

19 From six weeks onwards, the rate of withdrawal was

20 comparable between treatment groups. And as we do have

21 spirometry from week six, we can examine their final

22 FEV1 status and compare between treatment arms.

1   So each line on these figures represent a

2   patient who withdraw prematurely from the full analysis

3   set. DPM patients are shown on the left with blue

4   lines, and on the right control in green. It shows

5   their last FEV1 measure prior to withdrawal, either at

6   week six or 14. The average improvements from baseline

7   were greater in the DPM arm at 71.7 mLs, compared to

8   the average change of 6.7 mLs in the control arm.

9   So although we have no spirometry data in

10 patients prior to week six, this might also suggest

11 that some patients withdrawing early were not worsening

12 either.

13   Now, to reassure that the conclusion from the

14 primary analysis based upon the FAS population is still

15 valid, sensitivity analyses were conducted. And we

16 agree with the FDA that it is desirable to use the ITT

17 when evaluating the primary efficacy endpoint, and that

18 the missing data, as a result of differential dropouts,

19 should be accounted for.

20   Our sensitivity analysis does address this,

21 and the application of penalties to the MMRM model, and

22 the use of baseline observation carried forward, we

1 believe are particularly useful approaches.

2   Now, you may be aware that at the request of

3 FDA the National Research Council produced an expert

4 report on treatment of missing data in clinical trials,

5 a summary of which was published in The New England

6 Journal in October last year. The NRC acknowledged

7 that there is no universal method for handling missing

8 data, but they favored multiple imputation models,

9 because available information about the missing data

10 can be included into the final analysis set.

11   To assess robustness, they recommended patent

12 mixture models of sensitivity analysis. The NRC

13 considered that if the treatment effect can be shown to

14 be maintained, despite a range of clinically plausible

15 penalties, then the findings are robust.

16   Now, in keeping with NRC recommendations, our

17 sensitivity analysis allowed for different ways to

18 impute missing data that does include the whole ITT,

19 unlike the primary, which is based on the full analysis

20 set. The data were analyzed longitudinally over the

21 whole treatment period by MMRM, which included using

22 multiple imputation, and by matching the patients with

1 missing data with other patients who had similar

2 baseline features. The missing data could be imputed

3 in a meaningful manner.

4   Importantly, the patent mixture model, using

5 multiple imputation, included a penalty of 20 mLs for

6 every missed visit in subjects who withdrew from the

7 ITT population. So rather than model only imputing for

8 missing data, as I showed earlier, a penalty is applied

9 for every missing value. In this hypothetical example

10 shown here, a patient leaving before week six will

11 accumulate three penalties of 20 mLs each.

12   So I would like to run through the results

13 now of the sensitivity analysis. Firstly, this forest

14 plot prevents a sensitivity analysis of the primary

15 endpoint using MMRM over 26 weeks, first showing the

16 pre-planned primary estimate in the FAS population,

17 recognize that the potential for bias can never be

18 excluded.

19   Nevertheless, all of these sensitivity

20 analyses support the primary finding of a significant

21 increase in FEV1. Remember, the patent mixture model

22 of MMRM, using ITT, is highlighted here, penalizes

1   withdrawals by 20 mLs each missing visit, and does,

2   therefore, provide some reassurance regarding the

3   effect estimate over 26 weeks.

4   Now, we also explored the tipping point in

5   the ITT population at which DPM would no longer show a

6   significant effect. To do this, the penalty at each

7   missing time point is increased up to the point that

8   statistical significance is lost. Now, this table

9   shows what happens when we stress tested the data even

10 more. We increased the size of penalty shown in the

11 left-hand column for each missing visit in the patent

12 mixture model up until the point where significance is

13 lost.

14   The penalty would need to be more than 450

15 mLs at each missing time point before the effect

16 estimate is reduced to 55 mLs and is no longer

17 significant. This means that each patient leaving

18 before week six could be penalized by 1,350 mLs. A

19 tipping point requiring such a large volume does not

20 seem plausible.

21   We challenged the robustness even further,

22 again using the same patent mixture model, but this

1 time identifying a tipping point when only penalizing

2 the DPM arm but not control. Even applying this

3 extreme method, the tipping point needed to reach 150

4 mLs before significance was lost. Now, this means that

5 even patients withdrawing before week six in the

6 control arm carry no penalty at all, but, similarly,

7 DPM withdrawals being penalized by 450 mLs.

8   Data were also analyzed cross-sectionally by

9 ANVOCA at week 26, again using the ITT. And this

10 includes baseline observation carried forward, which

11 assumes the patients leaving early revert back to

12 baseline.

13   Now, I have already shown you that where data

14 is available after week six DPM patients who withdrew

15 were, on average, improving. BOCF is, therefore,

16 likely to be providing a conservative lower estimate of

17 overall treatment effect using the whole ITT.

18   So this forest plot represents the cross-

19 sectional analysis using ANCOVA in the whole ITT at

20 week 26. Now, this includes baseline observation

21 carried forward, conservatively assuming that patients

22 leaving early revert back to baseline. And yet this

1 remains meaningful and significant.

2   So although no end of sensitivity iterations

3 can ever provide certainty on the exact effect

4 estimate, there does seem to be a real effect that is

5 likely to be at least 60 mLs.

6   This study was, however, designed and powered

7 to look at FEV1 as a continuous variable, taking all

8 values into account. And this is widely recognized as

9 the best approach to assess a primary variable,

10 especially when there is no agreed threshold to define

11 a response.

12   The FDA's dichotomous approach of response or

13 no response assumes that there is a value above or

14 below which there is an effect. For example, someone

15 within a 99 mL improvement may be classed a non-

16 responder, but somebody with 101 mL improvement is

17 treated in the opposite way. And as a result, a huge

18 amount of power is lost.

19   The power using BOCF as a continuous variable

20 at week 26 to detect a 59 mL difference is 71 percent.

21 But the power decreases to only 24 percent when the

22 same data are dichotomized to evaluate a 100 mL

1 response.

2   Now, as withdrawal rates were quite high in

3 Study 301, and greater in the DPM arm, it is not

4 surprising that a significant difference at a single

5 26- week time point using a dichotomous approach wasn't

6 seen. Pharmaxis' view is that using the whole data

7 available in the ITT population at each time point is

8 more informative than basing any decision on arbitrary

9 thresholds of response at single time points, while

10 nevertheless recognizing that the responder approach

11 used in the FDA briefing book can provide supportive

12 perspective.

13   This table shows the FEV1 responder analysis,

14 but in the right-hand column includes the response

15 rates in patients who completed the 26-week study and

16 do, therefore, seem to tolerate DPM.

17   Now, while we cannot make claims of efficacy

18 based only on completers, importantly, DPM completers

19 are the group most likely to reflect the population

20 that would use DPM long term. The reality of managing

21 chronic conditions, in particular in CF, where there is

22 such a high pre-existing treatment burden, is that many

1 patients will not continue treatment long term if they

2 experience tolerability issues.

3   We acknowledge that DPM is not a treatment

4 for all patients. But as recognized by Dr. Ratjen, CF

5 treatment is routinely highly individualized.

6   I would now like to share some data using

7 secondary variables. The forced vital capacity shown

8 here followed a very similar pattern to FEV1, and these

9 mirror changes are consistent with DPM's intended

10 action; that is, FEV1 improvements are resulting from

11 improved airway clearance and unplugging.

12   Now, although FEV1 provides a useful

13 surrogate measure, exacerbations are also a key

14 variable in CF, and they cause challenges both acutely

15 and long term leading to permanent declines in lung

16 function.

17   Now, they are usually infrequent, though,

18 meaning that exacerbation is a challenging variable to

19 detect treatment difference. And it is simply

20 impractical in CF to undertake individual studies of

21 adequate size to detect clinically important reductions

22 as a primary endpoint.

1   We tried to use the most objective definition

2 of an exacerbation available to us at the time, and

3 that was as previously published by Fuchs. And this

4 required the occurrence of at least four of a possible

5 12 criteria, as well as intravenous antibiotic use.

6   The risk of patients experiencing at least

7 one exacerbation in the ITT population was reduced in a

8 post- hoc analysis by 35 percent compared to control.

9 There were also positive trends in rate reduction and

10 time to first event using hazard ratio.

11   Consistent with this trend was a 34 percent

12 lower rate of rescue antibiotic use, but no real

13 reduction in hospitalization rate. Presumably, a

14 reduction in exacerbation-related events is coming from

15 improved ventilation and less stagnant mucus as a

16 result of improved airway clearance. And, indeed, this

17 is supported with post-dose sputum weight from the ITT

18 population shown here, which was greater than control.

19   I will now discuss the study results of CF-

20 302. The primary endpoint of 302 was also changed from

21 baseline in FEV1 over the 26 weeks. Secondary

22 endpoints were hierarchical and included the

1 requirement of a significant primary effect. And I

2 will show you the P values for the pre-planned

3 analysis, but these are then for descriptive purposes

4 only.

5   Endpoints included are the lung function

6 parameters, FEV1, in rhDNase users, and sputum weight.

7 Exacerbations using the earlier Fuchs definition were

8 also explored.

9   Now, the intent to treat population comprised

10 of 305 patients and the full analysis set totaled 297

11 patients; 341 were screened, 14 patients had a failed

12 MTT, representing 4.1 percent of those screened.

13 Thirteen of the 318 randomized patients withdrew before

14 receiving study drug, giving us an ITT of 305, which

15 consisted of 184 patients in DPM and 121 from control.

16   Seven patients from DPM and one from control

17 withdrew prior to week six. So with few patients

18 withdrawing before week six, the full analysis set is

19 now based on 97.4 percent of the ITT. Between week six

20 and the end of the double-blind phase, a further 24

21 patients on DPM and 13 on control have withdrawn.

22   Now, but applying what we learned from CF-

1 301, the withdrawal rate was lower in this study. The

2 most common reasons for withdrawal were subjects

3 withdrawing consent and adverse events, both of which

4 were more frequent in the DPM arm.

5   Now, 302 included more younger patients than

6 301, but was, again, reasonably balanced between groups

7 and representative of the intended CF population. And

8 this study included U.S. centers, which contributed to

9 a higher rhDNase use overall. Antibiotic use was

10 similar and, again, reflected best standard of care.

11   So moving on to the results shown in the same

12 way as for 301, although numerically in favor of DPM in

13 Study 302, the difference in FEV1 by mLs between the

14 two treatment groups was not statistically significant.

15 Although as presented in the FDA briefing book, the

16 responder rates do support the true benefit.

17   Despite the primarily narrowly missing

18 statistical significance, the patent suggesting a

19 continued clinical benefit was also seen in this study.

20 Interestingly, the FDA's respond approach based at week

21 26 only is less conservative in this study, because the

22 treatment effect at this visit is quite a bit greater

1 than the average effect based on all three visits.

2   The sensitivity analysis seems less critical

3 to CF-302, and the lower withdrawal rate in this study

4 does mean that the MMRM method is more robust than in

5 301. The sensitivity analysis, therefore, runs

6 surprisingly perhaps quite consistent with the estimate

7 using the primary method. But as pointed out in the

8 previous slide, using ANCOVA at week 26 may not be so

9 conservative in this study.

10   The trends in 302 endpoints were mainly

11 supportive of a positive effect. Like 301, the forced

12 vital capacity followed the same pattern as FEV1 and is

13 consistent with an improved airway clearance. The risk

14 of patients experiencing at least one exacerbation

15 requiring IV antibiotics was reduced by 20 percent

16 compared to control, but this difference was not

17 significant. That was -- neither was statistically

18 significant. We again saw supportive trends of reduced

19 antibiotic use and a 25 percent reduction in

20 hospitalization rate.

21   And as shown in this figure, the post-dose

22 sputum weight was again greater in the DPM arm in this

65

1   study.

2   Now, as Study 302 was the only one to include

3   U.S. patients, I have included in this figure the post-

4   hoc findings from the U.S. subgroups shown on the

5   right- hand side. The change from baseline in the DPM

6   arm is remarkably consistent with both of the pivotal

7   studies overall. The data provides some reassurance

8   that the overall findings are applicable to CF patients

9   in the United States.

10   So moving on now to efficacy by subgroups.

11 Statistical significance should of course be based on

12 the overall population. And apart from the rhDNase

13 user subgroup, the trials were now powered to establish

14 efficacy by individual subgroups.

15   Now, since these are fundamentally identical

16 studies with comparable efficacy, I am going to present

17 the pooled data to maximize the size of subgroup

18 studied.

19   Now, as shown in this table, none of the

20 interaction terms were significant by subgroups. And

21 as this is consistent with the mode of action of

22 improved mucociliary clearance being applicable to all

1 CF patients studied, the possibility of a heterogeneous

2 therapeutic response seems small.

3   The subgroup FEV1 differences, compared to

4 control, nearly all trend in favor of DPM. And this

5 forest plot presents the FEV1 pooled data, shown

6 firstly as overall, then split by age group, then

7 rhDNase, gender, and, lastly, by severity based upon

8 FEV1 percent predicted at baseline. And almost all

9 favored DPM except in the final subgroup, FEV1, 40

10 percent predicted or less.

11   Now, confidence intervals by severity do all

12 overlap, and there is no pattern of reducing effect

13 with worsening severity, and some variability is

14 expected. But the data -- so the data do not suggest a

15 heterogeneous treatment. Nevertheless, there was a

16 suggestion of less effect in the subgroup studied below

17 40 percent predicted.

18   Now, you have been specifically asked to

19 consider benefit by age group, but the overlapping

20 confidence intervals and lack of significant

21 interaction term by age does not support a real

22 difference in effect between the age groups, although,

1 as expected in children with CF, variability was

2 greater in younger patients.

3   So finally, then, to sum up. The data shows

4 sustained and meaningful FEV1 improvements in CF

5 patients age six years and above, and that these

6 improvements are consistent with the mechanism of

7 action as supported by other improvements in

8 exacerbation risk as well as forced vital capacity and

9 sputum weight.

10   Studies in this orphan disease are

11 challenging, and any decision regarding useful effect

12 really should be interpreted based on the entirety of

13 evidence. Furthermore, DPM's useful effect is seen on

14 top of standard care in patients both above and below

15 18 years of age in this orphan disease.

16   So thank you, and I will now pass over to Dr.

17 Charlton to present the safety data. Safety

18   DR. CHARLTON: Thank you. I am Brett

19 Charlton, medical director at Pharmaxis.

20   The DPM safety profile has been well

21 characterized over three Phase II and two Phase III

22 studies in 713 CF patients, including 335 children.

1   These studies have included a diverse range of patient

2   demographics, seeing similar results regardless of age

3   or gender.

4   The Phase III cystic fibrosis data is a large

5   safety data set for this orphan population. Five

6   hundred forty-one subjects were exposed to DPM,

7   including 361 subjects during the double-blind phase

8   and an additional 180 subjects changing from control to

9   DPM during the open-label extension.

10   In total, there has been 370 patient-years of

11 exposure to DPM. Also included in the safety program

12 were 240 patients with at least 48 weeks of exposure

13 during which no new safety signals became apparent.

14 The data from these controlled studies best represents

15 the safety profile of DPM.

16   We will focus this safety presentation on the

17 issues highlighted by the FDA in their briefing book.

18 First, the active and only ingredient in each DPM

19 capsule is mannitol, which is generally recognized as a

20 safe product. Because the dosage is much less than

21 allowable dietary intake, DPM safety is focused on

22 local lung effects. As noted by the FDA, the extensive

1 non-clinical data support the safety of DPM for its

2 intended use, so I will proceed to clinical data.

3   Let's first briefly address laboratory

4 findings, including sputum microbiology. Clinical

5 parameters and laboratory measures were monitored at

6 each study visit. Overall, laboratory abnormalities

7 were similar in both treatment groups and were

8 attributed by the investigator to CF-related disease.

9 Infections in the sputum were of interest, since

10 infections are common in cystic fibrosis.

11   In addition, there was a hypothesized risk

12 that inhaled mannitol could lead to infections of the

13 respiratory tract. Therefore, we actively investigated

14 this situation. However, sputum flora was unchanged by

15 DPM treatment. Qualitative sputum microbiology showed

16 no overall change in growth and no difference in growth

17 between DPM and control.

18   So now let's address adverse events. This

19 table shows the most common adverse events reported.

20 The overall event rate is similar across the treatment

21 arms, and for the most part the type of events are what

22 would be expected in a CF population.

1   Most of these events were more frequent on

2 control than DPM. When looking at the adverse events

3 occurring with at least a one percent greater frequency

4 in the DPM group than in the control group, we see

5 cough, pharyngolaryngeal pain, hemoptysis, and

6 vomiting. As noted in the FDA briefing book, most of

7 the adverse events seen were of either mild or moderate

8 intensity and were likely related to tolerability and

9 ability to remain on therapy.

10   This table shows all of the serious adverse

11 events with an incidence greater than one percent by

12 preferred term. As you can see, the overall incidence

13 of serious adverse events was lower in the DPM arm than

14 in the control arm. Hemoptysis was the only serious

15 adverse event that was more frequent in the DPM group.

16 Hemoptysis will be discussed in more detail later in

17 the presentation.

18   Here we see the most common adverse events

19 that led to discontinuation. Discontinuation due to

20 adverse events was more frequent in the DPM group than

21 control; 11.4 percent of DPM patients versus 6.3

22 percent of control patients discontinued from the study

1 due to an adverse event.

2   The causes for discontinuation in at least

3 one percent of subjects were cough, condition

4 aggravated, and hemoptysis. All cases resolved

5 following discontinuation.

6   Although a discontinuation due to condition

7 aggravated appears more common on DPM, the overall

8 incidence was lower in DPM-treated patients. The

9 overall adverse event profile is similar across all age

10 groups when we group patients as those age six to 17

11 years, and adults age 18 years and above.

12   There are no major differences in the

13 relative incidence of overall adverse events between

14 the group age six to 17 years and the adult population.

15 Importantly, the incidence of serious adverse events

16 was lower on DPM than control in six- to 17-year-olds

17 and adult patients. More DPM than control subjects

18 withdrew due to adverse events in both age groups.

19   Based on the clinical experience with

20 mannitol to date, we identified several adverse events

21 for special review. These are either known adverse

22 events related to mannitol's mechanism of action and

1 mode of delivery or adverse events associated with

2 cystic fibrosis.

3   We will focus on bronchospasm, cough, and

4 hemoptysis. Firstly, let's look at bronchospasm. A

5 mannitol tolerance test was undertaken at screening to

6 identify patients with bronchial hyperresponsiveness.

7 FEV1 was recorded as a direct measure of

8 bronchoconstriction. Seven hundred nineteen patients

9 were screened using the MTT for the Phase III studies.

10   Importantly, the falls in FEV1 measured

11 during the MTT were not large. 5.7 percent of patients

12 had falls greater than 20 percent, which met the

13 criteria for a test failure. In these patients with a

14 failed test, the mean fall in FEV1 was 25.6 percent.

15   Now let's look at bronchospasm events during

16 treatment. Adverse events possibly associated with

17 bronchoconstriction on DPM during the treatment period

18 were not frequent, not severe, and were generally

19 transient. As already noted by the FDA, the frequency

20 of bronchoconstriction events was similar in DPM and

21 control groups.

22   Bronchospasm itself was a rare event reported

1 in only two DPM patients. Because of the known

2 association between DPM and potential

3 bronchoconstriction risk, the label recommends a

4 mandatory MTT to exclude patients with bronchial

5 hyperreactivity from any further treatment.

6   Although the subject risk of bronchospasm for

7 those patients passing the MTT appears low,

8 bronchospasm itself can be a serious event. In light

9 of this, we have requested a boxed warning on the

10 proposed label for DPM to include risk of severe

11 bronchospasm.

12   Now let's move to cough. Cough was reported

13 in 21.1 percent of patients in the DPM group compared

14 to 16.7 percent of patients in the control group.

15 Cough was reported as a severe event in 2.2 percent of

16 subjects in the DPM group, and 1.7 percent of subjects

17 in the control group. There were no SAEs of cough

18 during the blinded studies.

19   Cough led to discontinuation from the study

20 in five percent of subjects in the DPM group, and in

21 2.5 percent of subjects in the control group. However,

22 most cough events were not severe. Cough, along with

1 pharyngolaryngeal pain, appears to be a tolerability

2 issue rather than a safety one.

3   Now let's consider hemoptysis. Hemoptysis is

4 a common event in cystic fibrosis and is frequently

5 associated with pulmonary exacerbations. Treating

6 physicians are experienced in the recognition and

7 treatment of hemoptysis using established management

8 guidelines.

9   The amount of blood in the sputum is

10 generally less than five mLs but can range to large

11 amounts. Although the majority of hemoptysis events are

12 usually mild, the incidence of hemoptysis has been

13 reported to increase with disease severity and patient

14 age. The main risk is with massive hemoptysis events,

15 which are infrequent but can be fatal. Notably, there

16 were no fatalities throughout the trial program.

17   Hemoptysis adverse events were reported more

18 frequently on DPM than control. Overall, 9.4 percent

19 of patients on DPM reported hemoptysis compared to 5.4

20 percent of patients on control. The median duration of

21 all events was less than one day in both treatment

22 groups. All events resolved, regardless of treatment

1 allocation.

2   This table shows the breakdown of hemoptysis

3 events by severity. The majority of hemoptysis adverse

4 events were reported as either mild or moderate

5 severity by the cystic fibrosis investigator. This

6 figure shows the relative incidence of hemoptysis

7 adverse events between DPM and control groups split by

8 the subject's baseline FEV1.

9   The overall incidence of hemoptysis adverse

10 events increased with increasing disease severity and

11 was highest in those patients with FEV1 below 40

12 percent.

13   It should also be noted that hemoptysis is

14 frequently a component of exacerbations. These were

15 not always reported as adverse events. Because study

16 investigators were not specifically instructed to

17 report all hemoptysis episodes as adverse events, a

18 number of hemoptysis episodes occurring as a part of an

19 exacerbation were not separately reported as adverse

20 events.

21   As noted by the FDA in their briefing book,

22 it could be considered more accurate and meaningful to

1 consider these episodes, as well as the adverse events,

2 to determine the true incidence of hemoptysis.

3 However, it is recognized that those episodes only

4 reported as adverse events may be more clinically

5 significant.

6   Consequently, we present hemoptysis adverse

7 events and those episodes reported as part of an

8 exacerbation separately, as well as presenting the

9 combined incidence. For the overall safety population,

10 the incidence of hemoptysis adverse events was 9.4

11 percent on DPM and 5.4 percent on control.

12   For those hemoptysis episodes associated with

13 exacerbations, the incidence was 3.9 percent and 7.9

14 percent for DPM and control, respectively. The total

15 incidence of hemoptysis episodes, including those

16 reported as a hemoptysis adverse event and those only

17 reported as part of an exacerbation, was comparable

18 between arms.

19   Now, look at this same data but split by ages

20 six to 17 and 18 years and above. There is an increase

21 in hemoptysis adverse events on DPM in six- to 17-year-

22 olds, with an incidence of 7.8 percent on DPM and 1.9

1 percent on control.

2   As with the overall population, there were a

3 number of hemoptysis events in this age group that were

4 reported as part of an exacerbation, but not as a

5 hemoptysis adverse event, accounting for 2.6 percent on

6 DPM and 5.7 percent on control.

7   We agree with the FDA that there is a signal

8 for hemoptysis in patients age six to 17 years, and we

9 recognize that in these younger patients this has

10 clinical significance. In adults, the incidence of

11 hemoptysis seems comparable for DPM and control.

12   We do not know if hemoptysis is only limited

13 to patients at risk. However, we find that of the 16

14 patients age six to 17 years experiencing hemoptysis

15 during the studies all had risk factors. These

16 included reduced lung function with almost half having

17 an FEV1 less than 50 percent. Of the adverse events,

18 10 of the 12 were mild to moderate in severity.

19   Most hemoptysis events occurred as part of a

20 pulmonary exacerbation. And all patients had either a

21 previous history of hemoptysis or infectious risk

22 factors. Importantly, none of these subjects withdrew

1 from the study.

2   Of the 12 hemoptysis adverse events in six-

3 to 17-year-olds, 10 were considered mild to moderate,

4 while two were severe. Three were considered serious

5 due to hospitalization for the associated exacerbation.

6 All of the events resolved, and no patients withdrew

7 from the studies due to hemoptysis.

8   In the 26-week clinical trials, the incidence

9 of massive hemoptysis was comparable between DPM and

10 control. There was one reported massive hemoptysis

11 event that occurred in the open-label trial two weeks

12 after completion of DPM treatment. Overall, there are

13 very few events, but the rates were similar to the six-

14 month rates reported in other published sources.

15   So there appears to be a signal for increased

16 risk of hemoptysis on DPM, although the incidence of

17 massive events is not increased. The increased

18 hemoptysis signal appears to be associated more with

19 the six to 17 year age group.

20   Because hemoptysis is a recognized risk with

21 DPM, we are proposing to include relevant text in the

22 warnings and precautions section of the prescribing

1 information. This will alert physicians to the risks

2 and provide guidance regarding the need for careful

3 monitoring.

4   We would propose the clinical decisions,

5 including discontinuation of treatment, be based on

6 current CF Foundation guidelines. This would include

7 withholding DPM in the event of massive hemoptysis. In

8 addition, because of greater uncertainty surrounding

9 benefit/risk in patients with FEV1 less than 40

10 percent, it is to be recommended that there be a limit

11 -- this be a limitation to the indicated use.

12   Risk minimization efforts will continue to

13 focus on correct inhaler techniques to minimize

14 tolerability issues and associated adverse events. We

15 will also continue to educate patients on the

16 importance of adherence. We will accomplish this by

17 limiting distribution through established CF pharmacies

18 and certified CF centers who will provide point-of-care

19 support when initiating therapy.

20   Medical science liaison staff will provide

21 guidance on correct use of the MTT and minimization and

22 management of hemoptysis directly to health care

1 professionals. And beyond our standard

2 pharmacovigilance activities, we will collect and

3 assess detailed questionnaire information for

4 hemoptysis events, which will be periodically analyzed

5 to guide risk assessment.

6   We are also evaluating supportive post-

7 approval activities in pediatric patients that will

8 allow us to investigate the hemoptysis risk. We are

9 committed to doing a program to assess the pediatric

10 patients. Based on discussions with cystic fibrosis

11 experts, we believe that a registry program is the most

12 appropriate way to gather hemoptysis data.

13   We are exploring with the Cystic Fibrosis

14 Foundation, who have the most comprehensive database

15 available in CF, about a format similar to the registry

16 already implemented in Europe. It is our intention to

17 discuss these activities with the FDA, along with the

18 feedback from our discussions today.

19   So to summarize the safety of DPM, an

20 extensive body of data describes the DPM safety

21 profile. The active ingredient is mannitol, which is

22 generally recognized as safe and supported by years of

1 safety experience.

2   The patent of adverse events observed in

3 patients was consistent with the disease state and with

4 the mode of study drug administration. While most

5 adverse events represent tolerability issues,

6 hemoptysis is identified as an adverse event of

7 interest, particularly in the six to 17 age group.

8   Although CF clinicians consider hemoptysis to

9 be manageable, we will directly address the safety

10 concern of hemoptysis within the label and as part of

11 our post- approval activities.

12   Thank you. I will now turn the presentation

13 over to Dr. Flume. Risk/Benefit and Clinical

14 Perspective

15   DR. FLUME: Thank you. I disclose that I was

16 investigator on one of the trials presented today, and

17 I am being compensated for my time and travel.

18   So I come to you as a clinician with

19 considerable experience in cystic fibrosis. I have

20 more than 20 years of clinical experience, extensive

21 participation in CF clinical trials, and I was one of

22 the co-chairs of the original Pulmonary Guidelines

 1 Committee.

 2   You have heard the pathogenesis of CF lung

 3 disease, and it is that vicious cycle of infection,

 4 inflammation, and obstruction that causes progressive

 5 decline in lung function and eventual respiratory

 6 failure.

 7   Here are demonstrated data from an actual

 8 patient seen at our center, and you can see that this

 9 young adult suffers acute drops in lung function.

10 These are typical of pulmonary exacerbations, and there

11 is an overall downward slope in lung function. So our

12 goals of therapy when we see patients like this are to

13 prevent these exacerbations and to slow the rate of

14 decline of lung function.

15   Here again is the pathophysiology of lung

16 disease in cystic fibrosis. I cannot stress enough the

17 importance of clearance of airway secretions. Not only

18 does this relieve some of the airways obstruction, but

19 every drop of sputum contains millions of bacteria. So

20 coughing up a quarter cup of sputum unloads a lot of

21 infection as well as inflammation.

22   Better yet, we need therapies that address

83

1 the pathophysiology further upstream in the hopes of

2 reducing or preventing the vicious cycle of infection

3 and inflammation. So when I look at a new medication

4 for my patients, there are three essential questions

5 that I ask. What is the evidence for efficacy? What is

6 the safety profile? And if the drug looks attractive

7 for my patients, how will I introduce it into their

8 regimen?

9   So let's look at DPM with respect to these

10 questions. Shown here are the changes in FEV1 from the

11 two trials. As you can see, there is an improvement in

12 lung function from baseline with the use of DPM by

13 about 110 to 120 mLs, or an overall treatment effect of

14 54 to 83 mLs when compared to the control. These are

15 clinically meaningful differences.

16   While the treated groups look similar between

17 the studies, the smaller treatment effect that we see

18 in CF-302 appears to be mainly the result of changes in

19 the control group.

20   With respect to the concern about the

21 dropouts in Study 301, I feel comfortable that DPM

22 provides efficacy as shown in the tipping point

1   analysis presented by Dr. Fox. The amount of lung

2   function that would have needed to drop to negate that

3   statistical significance is unrealistic. It is just

4   too much more than what we typically see in clinical

5   practice.

6   This treatment effect analysis is the way

7   that we typically evaluate CF results, and let me put

8   that into perspective by comparing these results to

9   those of other medications that we routinely use in the

10 care of our CF patients.

11   The first approved drug for the treatment of

12 CF lung disease was rhDNase, and that was studied in

13 the early 1990s. The treatment effect on lung function

14 from the Phase III studies was 119 mLs. I want you to

15 note that we had very little else to use in our

16 patients at this time.

17   Next came aerosolized antibiotic tobramycin.

18 The Phase III trials that were performed in the latter

19 part of the '90s saw a treatment effect of 142 mLs, yet

20 a more recent study of tobramycin published in 2011

21 shows a less robust treatment effect. This is likely

22 because of diminishing effects of inhaled antibiotics

1 over time, or because we currently use many other

2 medications to treat our patients with CF lung disease,

3 such as rhDNase, hypertonic saline, chronic macrolides,

4 and aerosol antibiotics, all of which are recommended

5 in the CF pulmonary guidelines.

6   These guidelines also recommend hypertonic

7 saline based on improvement in lung function and a

8 reduction in pulmonary exacerbations, with a treatment

9 effect of 68 mLs. So compared to these pivotal CF

10 studies, the treatment effect with DPM appears

11 consistent with these other therapies commonly used to

12 treat CF lung disease, supporting a clinically

13 meaningful treatment response.

14   And I again want to stress that the patients

15 in the DPM studies had a high rate of concomitant

16 medication use, which is very different from these

17 pivotal trials of rhDNase, inhaled tobramycin, and even

18 the study of hypertonic saline.

19   Here I show the reduction in the incidence of

20 exacerbations from these same trials, and I think you

21 can see that the DPM results are again comparable to

22 what has been demonstrated with other CF medications.

1 And again I stress that patients on DPM had a high rate

2 of concomitant medication use, unlike these other

3 pivotal studies.

4   Now recall that the patients were offered

5 participation in an open-label extension. It is

6 impressive that most patients that completed the

7 double- blind phase and shown to tolerate DPM elected

8 to continue for an additional six months on inhaled

9 DPM. As with all CF therapies, some patients simply

10 don't tolerate DPM, and this is established early after

11 we start treatment.

12   So while recognizing that the patient numbers

13 have declined over time, and the data are uncontrolled

14 in the open-label phase, we see that most patients

15 remain on therapy. There are very few dropouts since

16 the tolerability has already been established, and the

17 patients maintain the benefit and lung function over

18 these additional six months.

19   Now let's address the question of safety, and

20 I want to focus on the two most relevant adverse events

21 with DPM, bronchospasm and hemoptysis. In these

22 trials, the mannitol tolerance test was used as part of

1 the screening process, and it appears to be a highly

2 effective method of screening.

3   Patients who fail the MTT were not allowed to

4 continue in the trial, and this resulted in less than

5 one percent of patients experiencing bronchospasm,

6 which supports the effectiveness of this strategy using

7 the MTT, as well as the use of an inhaled

8 bronchodilator prior to dosing. So for me the risk of

9 bronchospasm is not a major concern and appears

10 manageable.

11   So we move on to hemoptysis, and this is a

12 fairly common event for patients with CF, ranging from

13 scant, which is the most common, to massive, which is

14 far less common. Hemoptysis is typically associated

15 with infection and is a sign of pulmonary

16 exacerbations. We have general knowledge of how common

17 these events are in CF patients. A retrospective study

18 in Israel reported an overall incidence of hemoptysis

19 of nine percent.

20   In the previously mentioned pivotal clinical

21 trials, the reported rates of hemoptysis in the placebo

22 arms range from 21 to 31 percent in trials of at least

1 six months' duration. So the overall DPM rate does not

2 appear to be higher than what we typically see in our

3 patients.

4   But what about massive hemoptysis, an event

5 of much greater concern to the patient and clinician?

6 The rate of massive hemoptysis associated with DPM was

7 within the range that we have reported from our CF

8 patient registries. Hemoptysis is a common aspect of

9 CF lung disease, enough so that we generated CF

10 pulmonary guidelines dedicated to this complication.

11   Our CF clinicians monitor for events, and

12 when they see them they quantify the amount of

13 bleeding. The guidelines presented several

14 recommendations. Typically, physicians consider

15 hemoptysis as a manifestation of exacerbation and treat

16 it as such.

17   The guidelines recommend in the setting of

18 massive hemoptysis that we withhold certain therapies,

19 such as airway clearance therapies and aerosol

20 therapies, until the bleeding has resolved after which

21 time we would reinstitute those therapies.

22   So let's tackle the issue of hemoptysis in

1 children and adolescents in these studies head on.

2 There is a signal that hemoptysis occurs more often in

3 younger patients with DPM, even when exacerbations are

4 taken into account. But when you look at the adults,

5 there is no difference.

6   The children who had hemoptysis events also

7 had more severe lung disease, which is a known risk

8 factor for hemoptysis. Importantly, these patients had

9 more severe lung disease than we see in our average

10 pediatric CF population. The hemoptysis was not

11 persistent, and there were no cases of massive

12 hemoptysis.

13   No patients withdrew from the trial as a

14 result of the hemoptysis event. In addition, these

15 pediatric patients were shown to have an improvement in

16 lung function with a median improvement of 60 mLs. So

17 knowing all of this information, in a group of patients

18 with higher risk, how do I weigh the risk/benefit in

19 all children and adolescents with CF?

20   Pediatric patients should have the

21 opportunity to obtain the overall benefit in lung

22 function, and I believe that this outweighs an

1 acceptable risk.

2   Other than hemoptysis, the DPM adverse events

3 appear to be tolerability-related. And withdrawals in

4 CF clinical practice due to tolerability is commonly

5 seen with other aerosol therapies that we use in cystic

6 fibrosis. And this is why I find the completer

7 analysis compelling, as shown earlier by Dr. Fox,

8 showing that patients who stayed on therapy until the

9 end of 26 weeks benefitted from treatment.

10   So now that we find that DPM may prove safe

11 and effective, how do we think about introducing it to

12 our patients? Patients with CF have a significant

13 burden of treatment. As stated by Dr. Ratjen, these

14 burdens lead to barriers to adherence. So when we

15 introduce a new therapy, we must be cautious about

16 adding to their overall treatment burden.

17   You have already heard and seen what patients

18 endure on a typical day, but let me give you a real-

19 life example. I have a patient who tells me that in

20 order for her to complete all of her therapies, then

21 get ready and drive to work, she must awaken at 4:00

22 a.m., just so she can get there in time. Once she is

1 there, she gets 15- minute breaks, she gets a 30-minute

2 lunch, so what do you think her enthusiasm is to repeat

3 that treatment cycle when she gets home from work?

4   So our patients make choices every day about

5 their therapies, and unfortunately that choice may be

6 to skip them. So what we need, and what our patients

7 need, are options. We need to find the treatment

8 options that are best suited for each patient. The dry

9 powder option offers a low treatment burden, such as

10 portability, shorter treatment time, and it also fits

11 in the lifestyle of our patients as they often request

12 a more discreet therapy.

13   I would also like to acknowledge that there

14 are updated guidelines on chronic therapies by the CF

15 Foundation Pulmonary Guidelines Committee. I completed

16 my term on that Committee, and so I have nothing to

17 disclose with that respect. But just recently they

18 made this recommendation for the use of inhaled

19 mannitol. They have recommended that it be used in

20 patients six years and older who pass an MTT, and this

21 has been accepted for publication by the American

22 Journal of Respiratory and Critical Care Medicine.

1   The cornerstone of CF treatment for both

2   adult and pediatric patients is airway clearance. I

3   cannot stress the importance of this enough. So when

4   you look at the totality of the evidence for DPM, DPM

5   improves lung function and it reduces the incidence of

6   pulmonary exacerbations. These are clinically

7   meaningful improvements seen even in patients that are

8   already treated with the best standard of care.

9   The overall safety profile appears acceptable

10 to me. While DPM seems to increase the risk of

11 hemoptysis in younger patients, treating physicians

12 know how to monitor and how to address this event

13 should it occur. So I believe that DPM is a good option

14 for our patients, both young and old.   We do not

15 expect it to be the option for all of our patients, but

16 that is what we already know for every other medication

17 that we use to treat CF lung disease.

18   So I thank you for your attention, and I will

19 return the presentation to Dr. Fox.

20   DR. FOX: Thank you for your insights, Dr.

21 Flume. And thank you for your time and attention. Now

22 we look forward to answering your questions.

 1   DR. JACOBY: Questions from the Committee?

 2 Dr. Castile, were you -- I'm sorry. I thought you were

 3 -- Dr. Terry. Clarifying Questions to the Presenters

 4   DR. TERRY: I'd like to ask the question,

 5 perhaps I missed it, what was the dose in the mannitol

 6 tolerance test?

 7   DR. FOX: So the dose used in the mannitol

 8 tolerance test is the --

 9   DR. TERRY: Yeah.

10   DR. FOX: -- exactly the same dose as used in

11 the study up to -- it was taken up to 400 milligrams.

12   DR. TERRY: Did you ever consider after

13 people passed that then taking it up to the 600 dose,

14 which is the dose that induces bronchospasm, as a

15 further screen?

16   DR. FOX: We thought that the most

17 appropriate thing was to ensure that the dose that was

18 planned to be used in the population would be that of

19 400 milligrams, as opposed to the aridol test, which

20 was really looking at patients with suspected bronchial

21 hyperactivity as a confirmatory diagnosis. So I think

22 they were trying to achieve two different things, but I

1 think your question is well taken.

2   DR. JACOBY: I would like to follow up on

3 that, because what Dr. Terry was asked about was

4 something that I was also wondering about. The

5 description of the mannitol tolerance test in the

6 materials that you presented says, "Mannitol tolerance

7 test was conducted using sequential mannitol

8 administration with a target dose of 400 milligrams and

9 FEV1 measurements at three time points during the

10 tolerance test." And then you look for a 20 percent

11 fall.

12   So was it that you were giving -- you were

13 giving multiple capsules, obviously, and I would assume

14 that not everyone reached the 400 milligram dose. Is

15 that correct?

16   DR. FOX: That's correct.

17   DR. JACOBY: So do you have information on

18 what the distribution was of what -- what dose in those

19 that failed caused the 20 percent fall?

20   DR. FOX: Yes. What I'd like to do is

21 actually ask Dr. Charlton to come to the podium, if I

22 could, because I think it would be helpful for him to

1   sort of walk through that and to also look at the

2   different distributions.

3   Thank you.

4   DR. CHARLTON: I can show you here the

5   process for the test itself. So, yes, the 400

6   milligrams is given by inhalation of three capsules,

7   which is 120 milligrams, and then an FEV1 is measured.

8   And then a further 120 milligrams, FEV1 is measured

9   again, and then, finally, 160 milligrams and FEV1 is

10 again measured.

11   Now, if there is a fall of 20 percent in FEV1

12 prior to the 400 milligram total dose, that was a

13 failed test.

14   DR. JACOBY: Yes.

15   DR. CHARLTON: Yeah. I don't have the doses.

16 What I can show you is that -- well, what I can tell

17 you is what -- the 5.7 percent failed, and that the

18 mean fall was 25.6 percent. I do not immediately have

19 the data on the distribution.

20   DR. JACOBY: So, I'm sorry, I just want to

21 follow up on this, and then I'll --

22   DR. FOX: Is that something we could come

1 back with you after the break? Because I think we

2 could have the --

3   DR. JACOBY: Oh, absolutely.

4   DR. FOX: -- distribution data for that,

5 yeah.

6   DR. JACOBY: Right. But let me just ask

7 this. I think that the question that Dr. Terry was

8 getting at, and the thing that I was thinking about, is

9 it looks like the -- from the data that you presented,

10 the incidence of bronchospasm in properly screened

11 patients is low. And the thing that one might be

12 concerned about is with general release of this

13 inhaler, people being treated without appropriate

14 screening, for one reason or another, where the

15 screening was not done properly or something like that.

16   And so how bad can this be? There is a 25

17 percent fall in FEV1 among the ones that failed, but

18 that is presumably not people taking 400 milligrams of

19 mannitol. That is distributed among the doses at which

20 they failed.

21   So perhaps anecdotally, do we know, what is

22 the worst-looking reaction in a failed mannitol

1 tolerance test? Do these people get better very

2 quickly with bronchodilators? How bad --

3   DR. FOX: Sure. Understood.

4   DR. JACOBY: How bad -- what is the worst-

5 case scenario?

6   DR. FOX: Understood. So, again, I'll ask

7 Dr. Charlton to talk through that, including perhaps

8 some information on one of the Phase II studies where

9 patients were not pre-treated with the bronchodilator

10 for -- in cystic fibrosis. That would be useful, too.

11   DR. CHARLTON: The bronchoconstriction caused

12 with mannitol we know from experience -- we have had a

13 lot of experience with aridol in patients with airways

14 hyperreactivity that the bronchoconstriction is

15 reversible with bronchodilator. It is fairly quickly

16 reversible.

17   The worst fall in the MTT in the trial

18 program was 53 percent, and that was in a patient that

19 recovered within 30 minutes with bronchodilator.

20   DR. JACOBY: Great. Thank you very much.

21   DR. FOX: And in terms of the -- sorry, Dr.

22 Charlton. Just in terms of the Phase II experience in

1 terms of some patients, do you have that data

2 available?

3   DR. CHARLTON: I should have that data.

4   DR. FOX: Yeah.

5   DR. CHARLTON: Yeah. An additional piece of

6 data is that during the Phase II program we did

7 actually screen using a higher dose. And 74 patients

8 were screened with an over 600 milligram dose, and in

9 fact they were screened without pre-bronchodilator.

10 And the largest fall in these patients was 25 percent.

11 So even without pre-bronchodilator, and with a larger

12 dose, in a CF population equivalent to what was studied

13 in the Phase III trials, large falls are not a common

14 outcome.

15   DR. JACOBY: Just so I'm clear as to what you

16 did in this study, that's presumably also not just

17 giving 635 milligrams to people. It's a graded --

18   DR. CHARLTON: If they had a positive test

19 before --

20   DR. JACOBY: Yes.

21   DR. CHARLTON: -- they reached 600, yes.

22   DR. JACOBY: Yes.

1   DR. CHARLTON: Yes, that was positive.

2   DR. JACOBY: Okay. Good. Dr. Wagener?

3   DR. WAGENER: Just following on the slide you

4 just had up there, there were about 30 percent of

5 patients had a 15 percent fall. Did you look at what

6 percent had a 10 percent fall? Which is closer to the

7 variability of the test, at least in the pediatric age

8 group?

9   DR. CHARLTON: We did look -- in the Phase

10 III studies, we did actually look at the group of

11 patients that had greater than 10 percent fall versus

12 the group of patients that had less than 10 percent

13 fall. I'm not sure if we can bring that data up.

14   And what we looked at was the incidence of

15 bronchoconstriction events during the study, and

16 whether the MTT was predicting who was more likely to

17 have bronchoconstriction events. And what we can see

18 is that falls of greater than/less than 10 percent were

19 split about 50/50 during the MTT.

20   And the incidence of AEs -- sorry -- the

21 incidence -- what this shows is that the incidence of

22 AEs in patients that had less than 10 percent fall was

1 equivalent to the incidence of AEs in patients that had

2 a greater than 10 percent fall. So that the level of

3 fall during the MTT was not associated with subsequent.

4   DR. JACOBY: Dr. Castile?

5   DR. CASTILE: Just as a point of

6 clarification, when you do the MTT, do you pre-treat

7 with albuterol? In reading, I thought the answer was

8 no, but I thought I just heard the implication maybe

9 that that wasn't the answer. Just clarify that for me.

10   DR. FOX: Yes, sir. So during the Phase III

11 clinical program patients were routinely both pre-

12 treated with a bronchodilator before the challenge test

13 and before every dose during the study. The exception

14 to that was in the Phase II data where patients were

15 not routinely pre-treated in every single study. So

16 the data that Dr. Charlton showed. But in our Phase

17 III study everyone was pre-treated.

18   DR. CASTILE: How long after pre-treatment

19 was the first dose of mannitol given?

20   DR. FOX: So, Dr. Charlton, do you know the

21 average time for that or --

22   DR. CASTILE: For testing going forward, we

1 are going to need those details.

2   DR. CHARLTON: During the trials, the short-

3 acting bronchodilator was given between five and 15

4 minutes before the administration of the mannitol. And

5 the default bronchodilator was four puffs of albuterol.

6   DR. CASTILE: So the 12 percent or so that

7 failed and didn't enter the trial were actually -- they

8 had greater than 20 percent declines in FEV1, despite

9 pre-treatment with four puffs of albuterol. Have I got

10 that right?

11   DR. CHARLTON: That's correct.

12   DR. FOX: No, that's not. So just to

13 clarify, there was a proportion of those patients,

14 around six percent of the patients, who were screened

15 actually had drops of more than 20 percent as the

16 reason for withdrawing. There were other patients who

17 also were not classed as a failed MTT test, but did not

18 complete the test, presumably more from tolerability

19 due to cough or not willing to go further.

20   But they were not withdrawn because of

21 spirometric-driven reasons. That was the rationale for

22 splitting those out, to try and understand what the

1 proportion was actually due to a lung function drop as

2 opposed to just not completing the test.

3   DR. CASTILE: Yeah. Well, I guess I made the

4 spurious assumption that if you couldn't get through

5 the test that was -- your lung function probably was

6 not improving.

7   DR. FOX: Sorry. I should have made that

8 clearer.

9   DR. CASTILE: So I guess the other question I

10 had when I read the test was, why did you pick 20

11 percent as a drop? I mean, generally, when we look at

12 reactivity or treatment we think about 10 percent

13 change, 10 to 12 percent change in FEV1 as a

14 significant change.

15   I, just as a clinician, was a little

16 concerned - - I would be concerned I guess about giving

17 a patient a drug that produced a 20 percent drop in

18 lung function twice a day, or between a 10 and 20

19 percent, because those patients, by the MTT, the way

20 you've done it, would qualify.

21   So, you know, and my further thought on that

22 was, gee, I'd really like to know, of those patients

1 who were really in the 10 to 20 percent range, were

2 they the ones that dropped out, had more adverse

3 events, or had no improvement? I mean, is there -- the

4 cutoff just seems high to me.

5   DR. FOX: So I think there are two elements

6 to that question, and then I will actually pass to I

7 think a clinical expert to comment. Perhaps Dr. Bilton

8 could comment in terms of the reason for the threshold

9 and the rationale for that.

10   I think first, though, that -- please recall

11 the drop in FEV1 after drug administration despite

12 having pre-dosed with albuterol is a very temporary

13 drop. And that normalizes within half an hour. This

14 isn't a permanent drop that continues throughout the

15 day. Remember, the effect that we are looking at is

16 trough levels after 12 hours. So that's an important

17 distinction I think.

18   The second thing is, yes, we did look at

19 patients who -- I mean, I think that's the right thing

20 to think about. Are the patients who had -- who were

21 more twitchy during the test, are they more likely to

22 have adverse events going forward? So that was

1 something we looked at, and Dr. Charlton showed you

2 that the adverse event rate was virtually identical in

3 those patients compared to those who had falls of less

4 than 10 percent.

5   And I think your second question, again, is

6 an important one. Can you predict patient's response

7 to therapy going forward based on reversibility going

8 forward? And the answer is, again, we looked at that,

9 and we didn't see -- we didn't see any evidence of

10 being able to predict who is going to respond based on

11 that.

12   Perhaps I could get some clinical perspective

13 from Dr. Bilton in terms of the rationale.

14   Thank you.

15   DR. BILTON: Thank you. I am Dr. Diana

16 Bilton. I am the Center Director at the Royal Brompton

17 in London. I look after 600 patients age 16 and above

18 in London.

19   So the challenge test is looking at safety.

20 But from the patient point of view, it is also looking

21 at their tolerability, and it is in fact standard to

22 look at an inhaled new treatment before sending a

1 patient off home with it, to check how they do, that

2 they can tolerate the drug, and to look at changes in

3 lung function. And the threshold of 20 percent is a

4 standard one in our CF practice.

5   And you will often find patients saying, "Oh,

6 I dropped by 21 percent, but I felt okay. Please can I

7 have the drug?" But we stick at 20 percent as a safety

8 limit. And some of the patients in my clinical

9 experience now in Europe using this drug would have

10 drops that are asymptomatic, and we are having to

11 discuss with them that 20 percent is our safety

12 threshold.

13   So I feel comfortable with the 20 percent.

14 Of course, that is in the context of it being

15 reversible as you sit with the patient, which these

16 are.

17   DR. CASTILE: In your clinical practice,

18 since you use this now, do you have concerns about

19 patients who have -- starting this drug in patients who

20 you already know have airway reactivity, either based

21 clinically on a clinical diagnosis of asthma or other

22 pulmonary function testing like albuterol

1 responsiveness that, you know, clearly demonstrates

2 they are reactive. Do you screen those patients, or do

3 you just go ahead and test them?

4   DR. BILTON: I think that's a really good and

5 important question. The difficulty is -- with cystic

6 fibrosis is that airway hyperresponsiveness can vary in

7 one patient. And clearly going into these trials my

8 concern was to be sure that there wasn't an increasing

9 incidence of bronchospasm as we went along. So that

10 although a patient may have passed the mannitol

11 tolerance test, there may be later adverse events, and

12 we weren't seeing that in the studies. And I haven't

13 seen it in clinical practice.

14   Checking with colleagues in Australia, their

15 experience is similar. We think the MTT selects out

16 the patients who should not get the treatment in terms

17 of safety with bronchospasm.

18   DR. FOX: So may I provide a further

19 clarification as well? Asthmatic or patients at least

20 with a diagnosis of asthma were not excluded from these

21 studies. Obviously, the diagnosis, as Dr. Bilton said,

22 is very difficult in CF patients. But patients were

1 not excluded, and in fact they were slightly more

2 numerically in the DPM arm than in the control arm,

3 patients with asthma history. And yet we still see the

4 results in terms of the ones that we do.

5   DR. JACOBY: Dr. Blake?

6   DR. BLAKE: My question follows along the

7 same topic, but I was really more interested in the

8 period of time for those patients who didn't reach that

9 six-week time point, and what exactly happened to them

10 during that time point, because you had, you know -- in

11 Study 301, you had 18 in the treatment group and five

12 in the placebo group who discontinued, and seven versus

13 one in the other study.

14   And I'm wondering, those people who came in

15 and had the tolerance test on the one specific day,

16 maybe they were feeling great that day and they

17 tolerated it well, but then over that six-week period,

18 you know, days weren't so good and they didn't tolerate

19 it so well.

20   And I'm trying to get at a way maybe to

21 better pick patients who are going to tolerate it for

22 the long run, so that they don't have to go through

1 this period, you know, where they are not doing well.

2   And I want to tie it into pediatric patients,

3 because I think that pediatric patients are going to be

4 more adherent with the drug and take it twice a day,

5 because the parent is going to give it to them,

6 certainly, up until the age about of 11 or 12, whereas

7 adults may make a decision one day or another not to

8 give it to themselves, because they may not be feeling

9 well.

10   And I just wonder for those children, can we

11 come up with a better way to predict those who are

12 going to tolerate it well for the long term?

13   DR. FOX: I think the answer is probably I

14 think that the test itself seems extremely effective at

15 filtering out patients who are at risk of bronchospasm.

16 That I think we can be reasonably confident with the

17 data that we have.

18   Can we filter out patients earlier? I think

19 that would be a clinical question. I would ask Dr.

20 Ratjen to come to -- as he is the pediatrician in the

21 group, to give you his clinical thoughts on that. I

22 think it would be a difficult challenge to know what to

1 do without actually trying the drug to identify.

2   DR. RATJEN: Yeah. I think it's an excellent

3 question, but I don't think we have the answer. It

4 would be nice to have an early marker that you could

5 use that would predict in terms of what the

6 tolerability would be subsequently. But I don't think

7 that the tolerance test that acutely assesses

8 bronchospasm is ideally suited to test for that. At

9 least the data from the trial is not necessarily

10 informative in that way.

11   DR. FOX: I think we did get some learnings,

12 though, from Study 301 where cough was one of the major

13 reasons for -- the most common adverse event for

14 leaving in that first six-week period was cough. And

15 we recognized that the rate at which you inhale

16 certainly is more likely to trigger cough.

17   Now, in the second study we did put

18 particular - - well, we did a few things. First of

19 all, we made sure that expectation was set for cough at

20 the beginning, but we also put more emphasis on

21 ensuring correct inhaler technique in that second

22 study. And also just simple tips like not just the

1 rate but also having a drink of water beforehand.

2   And that seemed to have an impact on the

3 lower withdrawal rate that we saw in the second study.

4 We saw a lower incidence of cough in that study, and we

5 saw a lower early withdrawal rate. It's hard to say

6 exactly whether what we did had a direct impact, but,

7 anecdotally, it seems that that would make sense. And

8 as a result of that, we are going to put specific

9 emphasis within our health education specifically about

10 how to manage cough and how to lessen the chance of it.

11   DR. BLAKE: So would you have recommendations

12 that patients hydrate themselves well before they take

13 the drug in the morning and in the evening?

14   DR. FOX: Certainly, I know anecdotally a lot

15 of patients say that they find that really helps. I

16 don't know if Dr. Bilton would like to comment on her

17 clinical experience of that.

18   DR. BLAKE: And are you going to recommend

19 that they take their medications in a certain order?

20   DR. FOX: Yes. Yes. Yes, we are. The DPM

21 should be taken before physiotherapy in particular. In

22 terms of relation to the other drugs, those would

 1 normally be the antibiotics, and so on, would be taken

 2 at the end of the regimen.

 3   DR. BILTON: Just a comment on the experience

 4 since the trial, but also to emphasize that we did

 5 learn from the UK and European experience before going

 6 to 302 in America that talking with the patients about

 7 having a drink before they have the inhaler, getting

 8 the flow rate right. If they do it too fast, they

 9 cough a lot more than they need to.

10   So we have learned and have an education

11 package within the clinic, so that patients tolerate

12 things better. And I feel that is a reason why the

13 withdrawal rate is different across the two studies,

14 and certainly in our clinical experience now is rather

15 different.

16   DR. BLAKE: Thank you.

17   DR. JACOBY: Dr. Terry?

18   DR. TERRY: I'd like to ask a question about

19 Slide C-49. That is the slide in which there are FEV1

20 changes from baseline to the time of withdrawal after

21 six weeks. On the left-hand side, there are a

22 significant number of individuals who had an

1 improvement in some -- a marked improvement in their

2 FEV1, but, nevertheless, they withdrew from the study.

3 And my question is, were the reasons that they withdrew

4 from the study different from those that didn't get any

5 apparent improvement in their

6 FEV1?

7   DR. FOX: Yeah. I think that's a very good

8 question. I don't think I have data on those specific

9 patients. That is something we could probably look at,

10 because certainly it doesn't look like it is a

11 worsening of disease. And it certainly sits with -- it

12 sits with the story of a number of patients leaving

13 because of cough. So I think that would be a really

14 good idea, to look at those specific patients in terms

15 of reasons for withdrawal.

16   DR. JACOBY: Dr. Wagener?

17   DR. WAGENER: There's some evidence in -- at

18 least in the pediatric population that chronic exposure

19 of the airway to irritants increases the development of

20 airway bronchoreactivity. Did you repeat the challenge

21 test at the end of the study to see whether or not

22 something might have changed?

 1   DR. FOX: Yes, we did. I'll ask Dr. Charlton

 2 to comment on that. We looked at two things. We

 3 looked at post exposure to the drug, but we also looked

 4 to how patients were reversed to albuterol as well

 5 prior to treatment as well, so we looked at it in the

 6 two ways.

 7   Would it be useful for Dr. Charlton to expand

 8 more on that, or would you like to see specific data on

 9 that? Would that be helpful? Dr. Charlton, please?

10   DR. CHARLTON: Yeah. I think the most

11 telling data is that we measured FEV1 before and after

12 administration of the DPM at the clinic visits

13 throughout the study. And you can see here that what

14 we have summarized, if we look at visit one to visit

15 three, which is 14 weeks, we can see that the

16 proportion of patients that were actually having an

17 increased fall in FEV1 following administration of DPM

18 was less than 50 percent. And in fact the number of

19 patients improving from visit one to visit three was

20 more than 50 percent.

21   The other important thing to note is that

22 this slide shows you the mean falls in FEV1 following

1 administration of DPM, and the negative number means

2 that they actually increased. So the mean was actually

3 an improvement in FEV1 both at visit one and at visit

4 three.

5   DR. JACOBY: Dr. Durmowicz?

6   DR. WAGENER: I guess just following on that,

7 so did any patients actually develop criteria that you

8 would call -- that would have excluded them from the

9 trial originally as they went through the study? In

10 other words, did anybody reach a point where late in

11 the study they had a 20 percent or greater fall when

12 they received mannitol?

13   DR. CHARLTON: Throughout the entire study on

14 DPM, 1.4 percent of subjects did recall a greater than

15 20 percent fall on one occasion compared to .4 percent

16 of subjects on control.

17   DR. JACOBY: Dr. Durmowicz?

18   DR. DURMOWICZ: I would just like to go back

19 to the mannitol tolerance test and take --

20 intolerability and make a couple of comments that might

21 at least point out some issues. And one is that we

22 have -- you know that the bar for a positive mannitol

1 tolerance test, after a pre-dose bronchodilator such as

2 albuterol, is minus 20 percent FEV1. It is notable

3 that the aridol test for bronchoreactivity, the bar for

4 discontinuation and saying you are hyperreactive is

5 minus 15 percent. So it's less.

6   The other issue -- and Dr. Blake alluded to

7 it - - is that I think people understand that once you

8 get past the mannitol tolerance test you are not out of

9 the woods. And you can see that by the great number of

10 differential dropouts in the treatment group over time

11 through the 26 weeks, not just at zero to six weeks but

12 throughout the whole program, compared to the control.

13   Now, that is a tolerability issue, which we

14 are discussing, and in some ways is a safety issue, in

15 what it means chronically to have these kind of

16 problems, if you sputter but don't quite have a minus

17 20 percent over time. But the issue -- and we discuss

18 it in the efficacy section, is that it messes around

19 with the efficacy determination because of these

20 differential dropouts. And that is why we are doing all

21 of these sensitivity analyses.

22   The point I want to make is regardless of the

1 number of sensitivity analyses we do, all of these

2 differential dropouts still create a population that is

3 different for comparison between the two study groups

4 ultimately. You have a population of patients taking

5 the drug that have screened out over 26 weeks all of

6 the non- tolerators. So these people have, you know,

7 lead pipes for airways and they are not going to get

8 reactive to this and they are going to tolerate it.

9   You are comparing that at the end of the day

10 now to a control group who may tolerate it -- you don't

11 know -- but there might be a lot of non-tolerators in

12 there. And that is not addressed by the sensitivity

13 analysis as far as I know.

14   So this tolerability issue is a safety issue,

15 but it also becomes -- it spills over to the efficacy

16 part.

17   That's all.

18   DR. JACOBY: Dr. Castile?

19   DR. CASTILE: Let me see if I can remember

20 what my question was. Oh. The first one -- I had two

21 questions, and then I'll shut up. For the clinicians,

22 since most of the effect is seen at six weeks, when you

 1 prescribe this, do you look at six weeks to decide

 2 whether to continue it or to discontinue it? So that's

 3 the first question.

 4   And just so I don't forget it, the second

 5 question was, I heard alluded to a Phase II trial 203

 6 that I didn't read about. And I just wondered if that

 7 could be briefly reviewed. I think it was -- it looked

 8 like a head-to-head comparison between rhDNase and

 9 mannitol.

10   DR. FOX: Sure. So I guess probably I'll do

11 that in reverse order, if I may actually, and get the

12 203 out of the way, and then I think probably the more

13 clinically relevant question is the six weeks related

14 to week 26. And then we can get a clinical perspective

15 on that as well.

16   So if we could first look to the data. This

17 was a study run by Andy Bush, Study 203. It was a

18 study that was stopped prematurely because of

19 enrollment difficulties, so it was very underpowered in

20 terms of making any conclusions. In the publication,

21 there was -- it was hypothesized whether the data

22 suggested that actually the combination of the two

1 treatments were not additive and that caused some

2 interest at the time.

3   Obviously, since then we have done two

4 studies with 300 patients in each one, and we have

5 shown significant benefit on top of rhDNase therapy.

6 But if I could just -- this is the data from that

7 study. The suggestions by Minasian et al. were based

8 just on the 12- week data, really large amounts of

9 variability with small numbers of patients. This is

10 looking at FEV1 on the Y- axis here, and you will see

11 that at week six there is actually no difference in

12 either of the three groups, either DNase users alone,

13 DPM alone, or a combination of the two.

14   And then after 12 weeks there were numerical

15 differences in the combination, but all overlapping,

16 small numbers of patients. That reasonably raised the

17 hypothesis about whether there was a less effect. I

18 think since then, though -- again, I will ask for

19 clinical comment in a moment -- I think, you know, the

20 two big studies used 300 each. That story has kind of

21 gone away.

22   I think the more interesting -- the

1 particularly interesting issue that you raise, though,

2 relates to data, perhaps what patients are doing at

3 week six, and does that inform us about what patients

4 are doing down the line at week 26?

5   Now, the data I showed you just by looking at

6 lines drawn across the time suggests that patients at

7 week six are kind of behaving the same at week 26. But

8 obviously this isn't about what is happening to the

9 individual patients. So the plot I have just put up

10 here specifically is actually looking at individual

11 patients from the pooled data, and it is looking at

12 what is happening to the changes at week six and how

13 they correlate with changes at week 26.

14   And actually there is a really pretty good

15 correlation there, and we took that actually a step

16 further to see if there could be utility in that

17 approach. And, in fact, a person with any improvement

18 at week six had a sensitivity and specificity of around

19 80 percent in terms of predicting whether they would

20 still have an improvement above zero at that time.

21   So equally you could be looking potentially

22 at patients who are not tolerating, are not improving,

1 at week six. There is an opportunity there to be

2 thinking about, well, if a patient is not improving at

3 week six, they are unlikely to be improving further

4 down the track.

5   So I would like Dr. Bilton to comment on the

6 data and where that may have a place.

7   DR. BILTON: Yes. Thank you. First, on the

8 DNase, I think the data in the studies is convincing

9 that this is an additive effect. It's two different

10 mechanisms of action for clearing sputum, and in

11 particular mannitol improving mucociliary clearance.

12   The six-week data is really interesting, and

13 it relates really to clinical practice that in CF at a

14 center -- if we have seen a patient and started them on

15 a new treatment, we would be bringing them back at a

16 reasonable interval for six or eight weeks. So it's

17 convenient to the patient to say, "How did you get on

18 this -- with this treatment? And what is your

19 response?"

20   And particularly with the adolescents and

21 young adults, they are going to tell us whether they --

22 this is a treatment they wish to continue, because as

1 you have already heard from Dr. Flume, there is a

2 significant burden of treatment. And the patients

3 quite rightly will decide their burden versus benefit

4 ratio.

5   I think what is attractive about inhaled

6 mannitol in the data here is that the six-week response

7 does predict a longer response. So as a physician, I

8 can have a reasonable conversation with patients and

9 parents about how things might go. And there is also

10 quite a nice correlation between that FEV1 response and

11 the exacerbation response which bears that out, which

12 is not there for some other drugs.

13   Thank you.

14   DR. JACOBY: Okay. Go ahead.

15   DR. CASTILE: Can I ask a follow-up? You

16 didn't really say whether you stopped the drug. If the

17 treatment is not having an effect, sort of alluding to

18 Felix Ratjen's concern, then we don't want to add to

19 their burden and there are other options. So, I mean,

20 do you use that as a pivotal point? And should that be

21 something we are recommending going forward, I guess is

22 what I was getting at.

 1   DR. BILTON: So I would entirely agree, if a

 2 patient comes back having not responded, or got worse,

 3 we are going to stop that drug, because even if I --

 4 well, I just wouldn't want to continue it, but they

 5 wouldn't either.

 6   DR. JACOBY: Dr. Herring?

 7   DR. HERRING: Thank you. I had first wanted

 8 to follow up on Dr. Blake's question and ask if there

 9 were any statistical models fit to the probability of

10 dropout to try to help predict the tolerability to the

11 400 milligram dose?

12   DR. FOX: I'm not aware of any. I'll just

13 check with my -- no, the statistician is saying no.

14 So, no, we haven't.

15   DR. HERRING: Okay. That could be useful

16 clinically down the road and as standard practice in

17 the analysis of missing data to compare responders and

18 non- responders across a variety of measured

19 characteristics. And in addition, you might be able to

20 use some of your data from the challenge test to

21 predict which subjects might be more likely to tolerate

22 the treatment. So I think you have some nice data

1 there that you could be -- that could be used for that

2 purpose.

3   DR. FOX: Sorry. If I could just jump in

4 there. So I think I misunderstood the question. So we

5 did look to see if we could identify responders as

6 opposed to tolerators, which is obviously a different

7 thing, because

8 --

9   DR. HERRING: Okay. So, yeah, so my language

10 was probably confusing.

11   DR. FOX: Well --

12   DR. HERRING: But when I say I guess --

13 people who did not drop out of the study or were not

14 forced to discontinue.

15   DR. FOX: Okay. So in that case, we haven't

16 -- we have looked for baseline features of response,

17 and we couldn't find any with adequate sensitivity or

18 specificity --

19   DR. HERRING: Okay.

20   DR. FOX: -- to be useful.

21   DR. HERRING: Yeah. So it might be useful to

22 see whether that initial challenge test gives you

1 information about who drops out or not. Then, I would

2 just like to ask a few more questions about the FAS,

3 the analysis subset. So that population is

4 problematic, as we know, in light of the differential

5 dropout on treatment that seems to be due in large part

6 to the adverse events and exacerbations.

7   So as was mentioned earlier, it's leaving you

8 with a healthier subset, presumably, in the DPM group.

9 And so with this type of missing data mechanism, the

10 missing data are likely to be what we call non-

11 ignorable

12 --

13   DR. FOX: Sure.

14   DR. HERRING: -- which means due to

15 unmeasured declines in FEV1. And so a mechanism like

16 that would not be apparent in a figure like the one you

17 showed in C-49, because it would be something you don't

18 see. You know, they have an adverse event after a

19 treatment and dropout, and you don't see that their

20 lung function has declined.

21   And so for the FAS population to be valid,

22 you really need to maintain that original

1 randomization, which more or less requires your dropout

2 to be independent of treatment and response. And so

3 based on the data presented, you know, it doesn't seem

4 likely that happens. And so I really like to see that

5 the sponsor did consider some simple approaches that

6 stress the study results in a variety of ways to try to

7 assess the robustness. I think that's very good.

8   But as far as I can tell, there are two

9 important issues that I don't see handled

10 simultaneously that I would like to see. The one issue

11 is, as mentioned in The New England Journal paper that

12 the sponsor cited in the slides by Rod Little,

13 propagating uncertainty.

14   So the simple imputation methods don't do

15 anything to account for the fact that we don't

16 propagate our uncertainty in knowing what the responses

17 would have been had we been able to see them. The

18 mixed model actually does that, but it assumes that the

19 data are missing at random, which is not likely. So

20 that's the other important issue is that the data are

21 likely to be missing not at random.

22   So I was wondering if -- there are a lot of

1 modeling approaches in the literature that can

2 accommodate both of those issues, propagation of

3 uncertainty and missing not at random, missing data

4 mechanism. And I wondered if the sponsor used any of

5 those, and, if so, what kind of assumptions or models,

6 you know, were made and what results they obtained?

7   DR. FOX: So first of all, I will pass over

8 obviously to --

9   DR. HERRING: Yeah.

10   DR. FOX: -- my statistician very shortly. I

11 think there are a couple of points I would like to

12 cover first of all. I mean, firstly, I think the

13 assertion that the -- Slide 49 when we showed the slide

14 first has no value, I would challenge that.

15   I do acknowledge what you're saying, that we

16 can't know exactly what these patients are doing. All

17 I'm saying is that based on their last FEV1, with some

18 of these patients having huge improvements, it seems

19 very unlikely that all of these patients are worsening.

20   So I think an assumption, therefore, of using

21 sensitivity models such as baseline observation carried

22 forward, which I have shared with you, it seems very

1 reasonable, therefore, to think that a simple approach

2 like baseline observation carried forward is a very

3 reasonable thing to do, because this data doesn't

4 suggest that this population is on average worsening.

5 It actually suggests there is a differential

6 improvement in the control -- in the DPM arm compared

7 to control.

8   DR. HERRING: So can I respond to that?

9   DR. FOX: Sure.

10   DR. HERRING: So the definition of "missing

11 not at random" is that you can't predict the

12 missingness based on -- only on the data you see. So

13 we can't see what happened to those --

14   DR. FOX: Absolutely.

15   DR. HERRING: -- lines when they disappear.

16 And so --

17   DR. FOX: Absolutely.

18   DR. HERRING: -- a plot like this could never

19 be used to rule out missing not at random.

20   DR. FOX: Absolutely.

21   DR. HERRING: So, you know, you could still

22 have a missing at random mechanism that shows declines.

1   DR. FOX: Absolutely.

2   DR. HERRING: So "missing at random" doesn't

3 necessarily mean they are doing -- doing better or

4 worse.

5   DR. FOX: Absolutely.

6   DR. HERRING: Now, about best observation

7 carried forward, in that Little paper they do not

8 recommend that method because it doesn't --

9   DR. FOX: That's true.

10   DR. HERRING: -- propagate uncertainty. So,

11 I mean -- not best, sorry, baseline observation carried

12 forward. So I agree with you that it is a conservative

13 approach in many ways. You're assuming they are not

14 any worse than they were when they started. But the P

15 value from that method will be too small, because it

16 doesn't take into account variance and knowing what

17 their actual lung function measurements were because we

18 don't know that. And that is discussed in that Little

19 New England Journal paper.

20   DR. FOX: Okay. So, again, you've taken me

21 above my technical expertise. I'd like to ask Dr. Day

22 to come to the podium. But I think just while he is

 1 coming there, I think just to point out, again, about

 2 the tipping point that we used with plausibility. So I

 3 think that's the -- we would have used a selection of

 4 sensitivity analysis.

 5   DR. DAY: Good morning. I'm Dr. Day, and I

 6 should disclose I have been compensated for my time and

 7 travel but nothing else.

 8   I agree with you about propagating the

 9 uncertainty. This is the multiple imputation approach,

10 which does propagate the uncertainty. I also agree

11 with you your concerns about bias in that. But what we

12 then did was use the tipping point analysis, which is

13 on top of the propagation -- propagating the

14 uncertainty.

15   So I think that we have adequately allowed

16 for the variance, which things like "based on

17 observation" don't do.

18   DR. HERRING: So in the multiple imputation

19 model, was that a missing at random mechanism?

20   DR. DAY: That's a missing at random, not

21 missing completely at random --

22   DR. HERRING: Right.

1   DR. DAY: -- but missing at random.

2   DR. HERRING: Right.

3   DR. DAY: But then we have added on to that,

4 or, I should illustrate subtracted from that, the

5 tipping point.

6   DR. HERRING: A fixed amount.

7   DR. DAY: Pardon?

8   DR. HERRING: The tipping point is a fixed

9 amount that -- I mean, it's a fixed offset, correct?

10   DR. DAY: It's a fixed offset, but against a

11 random imputation, if you --

12   DR. HERRING: Thank you.

13   DR. DAY: Thank you.

14   DR. JACOBY: Mr. Mullins?

15   MR. MULLINS: Yes. I have a couple of

16 questions for the sponsor in regards to certain safety

17 signals that -- just that I had questions about,

18 particularly in pediatrics. So I would like for you to

19 amplify the higher occurrence of hemoptysis within the

20 pediatric group. I was concerned about that.

21   And then, also, the occurrence of adverse

22 events of DPM versus control. Could you speak to that?

1   DR. FOX: Yeah. Sure. I think probably the

2 most useful thing to do would be, first of all, ask one

3 of my experts, Dr. Flume, who is an expert in

4 hemoptysis, could probably give you a much more useful

5 clinical picture.

6   DR. FLUME: Thank you. So we know a lot

7 about hemoptysis in cystic fibrosis patients. And it

8 is anecdotally a common event. It is associated with

9 more advanced stage lung disease, so we see it more

10 commonly in adult patients than we see in pediatric

11 patients.

12   And in terms of cataloguing the frequency of

13 those events, if I could have the slide from the core?

14 There are very few publications looking at this. Our

15 original publication using registry data was

16 specifically looking at massive hemoptysis, which is a

17 far more rare occurrence than is scant to mild

18 hemoptysis.

19   So in this particular slide, that first

20 paper, the Efrati paper, is a retrospective review of

21 data from an Israeli center looking at 440 patients,

22 identifying an incidence of nine percent of those

1 patients having hemoptysis. And in that population, 25

2 percent of them were under the age of 13. So that

3 gives us some indication of the frequency of these

4 events.

5   Now, that doesn't discount the finding of a

6 signal in this particular study. That obviously is

7 something that we acknowledge, that there is an event

8 there, although the events tend to be mild.

9   Now, because we recognize the frequency of

10 this event, as you can see in the placebo arms of those

11 pivotal trials a reported rate of 20 to 30 percent, the

12 CF Pulmonary Guidelines Committee generated a set of

13 recommendations to deal with that specific

14 complication.

15   Now, when we put together our guidelines, we

16 try to use evidence-based approaches to do that, but

17 there are no clinical trials looking at how to manage

18 hemoptysis that just don't exist. So what we used was

19 a consensus approach. But to avoid any kind of biases

20 being put into there, we used a Delphi approach with 20

21 centers, including both pediatric and adult centers,

22 and from that we were able to generate appropriate

1 recommendations for what to do in the setting of

2 hemoptysis, whether it be scant or massive hemoptysis.

3   MR. MULLINS: Could you expound on the higher

4 occurrence of hemoptysis within DPM patients versus

5 control?

6   DR. FLUME: Could I have the slide looking at

7 that? So this is separating the data out based on age.

8 This, too, was taken from the core set of slides that

9 we discussed earlier. And so what you see here

10 separating the pediatric population, so six- to 17-

11 year-olds, away from the adult population, what you see

12 is the total event -- number of events is 10.4 percent

13 in the pediatric patients who are getting the full dose

14 of DPM compared to 7.6 percent.

15   And recall that that includes the combination

16 of when the investigators reported it specifically as

17 an adverse event, but also those patients who had an

18 exacerbation in which they also recorded hemoptysis as

19 a feature. So what you see is a 10 versus eight

20 percent difference, so that gives a signal that perhaps

21 there might be some -- something to manage there.

22   But, again, I think this is a complication

1 which is well known by our pediatric clinicians.

2   MR. MULLINS: You seem rather high versus

3 control. You seem rather high versus control; that's

4 why

5 I --

6   DR. FLUME: I don't disagree that it's --

7   MR. MULLINS: Yeah.

8   DR. FLUME: -- greater. But I also would

9 argue that 10 percent to me for a mild complication is

10 an acceptable risk when you compare that to the overall

11 benefit in terms of improving lung function and

12 reducing pulmonary exacerbations.

13   MR. MULLINS: My second question was just

14 efficacy within that subgroup of pediatrics. Could you

15 speak to that also, because I have questions about

16 efficacy. Do you have the charge on that, on efficacy

17 within that subgroup --

18   DR. FLUME: I think --

19   MR. MULLINS: -- subpopulation?

20   DR. FLUME: -- what I'd like to do is invite

21 Dr. Fox to show the data that we have on efficacy

22 specific to that population.

1   MR. MULLINS: Thank you.

2   DR. FOX: Okay. So, first of all, if we go

3 back to my core slide where I showed -- so this is a

4 forest plot. So what this is looking at is the -- the

5 blobs are basically looking at the estimate of effect

6 size within each different subset of patients. So when

7 the -- they're on the right-hand side of the dotted

8 line they are in favor of DPM, and when they're on the

9 left they are in favor of control.

10   And the first cluster of data relates to

11 children, adolescents, and adults. And we can see that

12 in each case the blobs are on the right-hand side and

13 in favor. But visually you can see that the adolescent

14 group does appear to have a lesser effect.

15 Statistically, these aren't different, but you are

16 still left with the impression that -- is there

17 something going on in the adolescent population?

18   So what I'd like to share with you, and I

19 think it's perhaps useful, is the data where we break

20 out this data into the DPM arms versus control within

21 the individual study. So this is kind of an extension

22 of that data, and I'll just walk you through this if I

1 can.

2   So we've got DPM in blue, control in green,

3 on the Y-axis there we've got change in FEV1. We would

4 see a similar picture if we actually looked at this in

5 terms of FEV1 percent predicted as well. We've got

6 children on the left-hand side, then adolescents in

7 Studies 301/302 separately, and then we've got adults

8 on the right-hand side.

9   One of the features here we see is that in

10 terms of the DPM group, in terms of how they are doing,

11 actually the children and adolescents seem to be doing

12 better than adults, but so do the control group as

13 well. So there appears to be a large control effect, a

14 larger variability in that population. Nevertheless,

15 we are seeing in three of four of these arms benefit in

16 terms of the DPM arm.

17   Now, you have been asked to decide whether

18 there is adequate effect in these kids compared to the

19 safety signal, particularly in terms of hemoptysis.

20   We really sort of wanted to then look hard at

21 what was happening in this control group to see if we

22 could see what was happening there, and particularly in

1 terms of Study 302 adolescents, where it looks as if

2 the control group actually did numerically slightly

3 better. So the first thing we looked at was to see if

4 there were any randomization issues, whether there were

5 compliance issues, whether there were changing

6 concomitant medication issues over time. We couldn't

7 find anything there to explain that, so this may be

8 purely chance.

9   On the other hand, we do know that the

10 control dose is 50 milligrams of mannitol, so we can't

11 completely exclude that having an effect. But the

12 Phase II data suggests, again, that's not a good

13 reason. So we are really left still with, is this a

14 chance finding, so this just shows the -- so here we

15 should look at the dosing split by the age groups.

16 Again, we see a similar pattern.

17   There is nothing there to suggest that the 50

18 milligram dose that used in the Phase III studies, the

19 40 milligram dose used here in teenagers and kids, it

20 doesn't suggest that that's a cause either. So we're

21 left with this chance, always is something happening.

22   So the next thing we did was we looked to

1 see, well, was there a region effect? So we, first of

2 all, looked at the data by region. I think I will just

3 wait to share that with you.

4   And this shows the data for the overall data

5 by region, Europe; North America, which is the U.S.;

6 and some centers in Canada; Australasia, which is

7 Australia and New Zealand; and South America, which was

8 entirely made up of eight centers in Argentina.

9   And when we look at this pooled data, we see

10 remarkably consistent effect across all of the regions

11 apart from the eight Argentinian centers. Now,

12 obviously, this is very post-hoc. We are not making

13 any claims about efficacy here. The data of the two

14 pivotal studies is the data. You can't post-hoc select

15 those out and make claims.

16   But this did seem to be a very interesting

17 signal, particularly as Argentina was contributing the

18 highest proportion of teenagers in Study 302. They

19 were the big driver of the teenagers in Study 302.

20   So we said, okay, right, well, let's have a

21 look at -- let's look at the kids and adolescents in

22 Argentina. So if we compare on the left-hand side the

1 six- to 17-year-olds in Study 302 all together, that's

2 the 153 patients, and we've got a difference there of

3 29 mLs in Study 302.

4   Then, if we look at Argentina only, we see

5 that there was a favorable outcome in the control group

6 where the control group did 65 mLs better, such that if

7 post- hoc we had excluded the eight centers in

8 Argentina from this program, we would have seen a delta

9 of 80 mLs in children and adolescents in Study 302.

10 This is post-hoc, but this is what we found, so

11 hopefully that's useful.

12   DR. JACOBY: Dr. Tracy?

13   DR. TRACY: Thank you. My question is

14 obviously outside the study, but for the clinicians, do

15 you ever see your patients, before you use this

16 medication, forget to pre-medicate with albuterol? And

17 then -- that's the first question. And if they did

18 forget to pre-medicate with albuterol, what do you

19 think would happen?

20   DR. FOX: So I think I will ask Dr. Bilton

21 again if she has had experience in outside clinical --

22 outside the studies, first of all, and then perhaps as

1 Dr. Ratjen to comment as a pediatrician. That is also

2 an important consideration.

3   DR. BILTON: I think it's true that whatever

4 I advise patients to do on a busy day when they're

5 trying to get up and get to work, they are likely to

6 miss something out. I haven't had a patient come and

7 say, "Oh, I forgot my albuterol and then I felt

8 terrible after my aridol." That hasn't happened, but I

9 would expect that at some point, and possibly in the

10 trial as well, although patients say they are doing

11 things on busy days.

12   But certainly in my clinical practice we

13 haven't had a severe bronchospasm, and the Australian

14 colleagues who have been using it for longer than I

15 have have not had people collapsing with severe

16 bronchospasm because of that issue. That's all I can

17 tell you.

18   DR. JACOBY: Dr. Greenberger?

19   DR. GREENBERGER: This focuses on the

20 responses in the children and adolescents. And my

21 question is the data -- the FEV1s at the zero screening

22 versus V1, week one, which are used as baseline, are

1 you able to share with us those data, the one minus V0

2 in children, adolescents, as well as adults? And

3 preferably for 301 and 302.

4   DR. FOX: I can show you some data based on

5 the overall population. I don't have those split out.

6 That was based on a sensitivity analysis that we

7 discussed with FDA at our pre-NDA meeting. We were

8 advised by FDA I think very clearly that this was a

9 post-hoc analysis that wouldn't have been viewed

10 favorably.

11   And, therefore, we didn't include it in our

12 sensitivity analysis simply because it actually makes

13 our data look more favorable, so as a non-conservative

14 sensitivity analysis that we exclude it. But I can

15 certainly share that with you, what we saw.

16   This might be the most useful way of looking

17 at this. I think I need to walk you through it

18 carefully, though.

19   So what this is doing is showing in the solid

20 -- if we start with the solid blue line at the very

21 top, what we're seeing is the mannitol change from

22 screening in Study 302. And then if we look at the

1 solid red line directly -- sorry, underneath, we see

2 that the mannitol group, if we use change from

3 baseline, is virtually identical. It doesn't make any

4 difference whether you used a screening value or a

5 baseline value to look at your effect. It made no

6 difference.

7   If, on the other hand, you took the control

8 group shown in the blue dotted line, that plots out the

9 change from baseline visit one. So that's the data

10 that we are using and plan to use prospectively that we

11 are basing our 54 mL effect testament on.

12   If you look at the red dotted line, you will

13 see the -- what the control would have looked like if

14 we had, instead, used the control -- we had used the

15 screening value. And if we had used the screening

16 value instead, I can show you what the 302 data would

17 look like, if that's useful to you. But, obviously, it

18 would look less conservative and it would look -- it

19 would look very similar to 301.

20   So clearly this is a very non-conservative

21 sensitivity analysis. We appreciated the FDA's

22 feedback on that, and we chose not to include it on our

1 sensitivity analysis. But this is what it would look

2 like if we had used screening values instead of

3 baseline.

4   DR. JACOBY: Dr. Parad?

5   DR. GREENBERGER: Pardon me. My question is,

6 do you have this broken down for the three populations?

7   DR. FOX: No, sir. I don't.

8   DR. GREENBERGER: Because I'm wondering if

9 the changes occur in children and adolescents versus

10 adults.

11   DR. FOX: We did I think look at some of that

12 a couple of years ago, but obviously it was something

13 we have dropped since. I will try and see if I can get

14 that data during the break, and I will certainly make

15 an effort to. It does look like, though, the main --

16 the bigger driver is coming from the South American

17 centers, but, again, this could be a feature.

18   DR. JACOBY: Dr. Parad?

19   DR. PARAD: Okay. I've saved up three

20 questions. I'll get them off my chest at once. The

21 first one, following up on Dr. Castile's question a

22 bit, in terms of indications for initiating this

1 medication, will there be -- it looked like there was

2 some combination effect from using the DNase. Are you

3 proposing that clinicians add this to existing

4 hydrators or mucolytics? Or if a patient is on no

5 medications yet, what would the order of initiating

6 such drugs be? And what would be the indication for

7 actually starting this? What kind of symptomatology?

8 So that is question one.

9   Question two, going to the issue of children

10 again, it's a very broad age range in not a very large

11 number of patients. And children are different from

12 adults in lots of ways. And CF young children are

13 different from older CF patients.

14   So 80 mLs to me means a different thing in a

15 six-year-old than it does in a 40-year-old, because

16 their weight is probably four times different. But you

17 are expressing your primary outcome as an absolute

18 volume. So do you have the data also presented as

19 percent -- a delta in percent predicted FEV1, which

20 would correct for age. I mean, perhaps your data

21 actually suggests maybe we would see a bigger effect in

22 children who may have more reversible disease, or there

1 may be something different about them. Do you have the

2 data expressed in that way where we could look at

3 smaller children, at least below the adolescents?

4   And then, the last question is with regard to

5 duration of effect after stopping the drug in the

6 trial. Do you have data either from those who didn't go

7 into the open label after 26 weeks, or retesting after

8 the end of the 52-week period to see how rapidly --

9 what effect persisted or how rapid a decline there was

10 after stopping the drug?

11   DR. FOX: Gosh. That's quite a shopping

12 list. I might start backwards, if I may, and I might

13 have to come back with you for some clarifications on

14 those as well. Excuse me.

15   So in terms of the open-label data, we don't

16 have data of what happens when patients discontinue.

17 So time to -- do they go back to baseline or not? What

18 we do have is data on what happens to patients when

19 they go -- when they went into the open-label phase.

20 So this is data I'm sharing here from the two studies,

21 301 on the top, and this is based only on these

22 patients. You'll notice I have included the ends here.

1 This is based on the patients that went into the open-

2 label phase, and then we have tracked back to show you

3 what they were doing prior -- during the double-blind

4 as well.

5   So you will see that the pattern is quite

6 similar in both of these. Dr. Flume has already shown

7 you the blue line data, what happens to the active arm.

8 But also this slide shows you what happens to the

9 control patients shown in green during the double-blind

10 phase, and what happens when they switch to receive 400

11 milligrams.

12   So it's not the same, but it at least

13 provides some sort of very coarse open-label,

14 uncontrolled, with all of those caveats, sort of an

15 indication of what happens. But obviously that data

16 needs to be looked at with real caution I think.

17   So then going back to in terms of do we have

18 data by percent predicted, yes, we do, to account for

19 growth. That primary endpoint was based on using

20 milliliters. That was something, having discussed with

21 TDN, the most pure method to use because it is not

22 introducing other variables. But of course it is not

1 usefully accounting for age over a six-month study. So

2 this data is, instead, showing the pooled data both in

3 terms of mLs split by six to 11, 12 to 17, and 18 and

4 above, but also showing it in terms of percent

5 predicted change.

6   And you are absolutely right that when we

7 particularly look at the six- to 11-year-olds, when we

8 do take growth into account, then that data starts

9 looking more similar to adults as they've got smaller

10 lungs, and, therefore, they have relatively larger --

11 smaller changes in absolute terms. But in relative

12 terms, the changes are closer to the adult population.

13   Does that help address that particular

14 question, sir?

15   DR. PARAD: I am actually surprised there

16 isn't an even larger effect in a small group, but it

17 was perhaps not a very large number of children. Is

18 that --

19   DR. FOX: Well, yes. So about half the

20 patients were adults, reflecting the current

21 distribution of patients these days. So it did mean

22 that there was a smaller fraction of younger children.

1 The other issue, of course, with this study, by having

2 a cap of -- patients had to have FEV1s of less than 90

3 percent predicted at the start of the study. You had

4 automatically excluded the kids who, luckily, have

5 better -- less severe disease.

6   DR. PARAD: And then --

7   DR. FOX: And then there was a third

8 question, as I rustle through my paper. I think this

9 would be one that -- so this was in terms of the data

10 that we -- I mean, wouldn't it be useful to have a

11 pediatric opinion on that data as well, or you're happy

12 with that? So perhaps Dr. Ratjen could comment on that

13 as I think it is an important piece of it.

14   DR. RATJEN: Yeah. I think that there is

15 another way we could actually look at the data and look

16 at it per study, so you can look at the different age

17 groups and the different studies, similar to what has

18 been shown for the mLs overall. And that would -- this

19 is the slide for --

20   DR. FOX: And a change -- and there should be

21 on percent predictive --

22   DR. RATJEN: There should also be one in

1 percent, but it also already tells you that if you have

2 100 -- if you have a relatively high percent -- so if

3 you -- this is showing this here in terms of the

4 percent predicted in the different studies in the

5 different age groups.

6   And certainly for 302 there seemed to be a

7 higher effect in the 400 milligram group, and the --

8 and in 301, the effect was similar to what was seen in

9 adults. So I think the issues about the control group

10 have already been addressed, but if you look at the

11 change versus baseline that would support this notion,

12 that if you -- and this discussion of what is the

13 better way to look at it is -- has been ongoing in the

14 CF field, and many of us pediatricians feel stronger

15 about the percent predicted than the mLs.

16   DR. JACOBY: Thank you. And last question

17 from Dr. Blake.

18   DR. FOX: Thank you. And I think the last

19 one, if I could go back to -- sorry, sorry.

20   DR. JACOBY: I'm sorry. Perhaps we can

21 follow up on --

22   DR. FOX: Okay. Sure.

1   DR. JACOBY: Dr. Blake?

2   DR. BLAKE: This is more of a comment than a

3   question. And, again, it just goes back to the signal

4   for hemoptysis in the children. And, again, I go back

5   to the parents of young children under the age of 11

6   are very motivated to give their children their CF

7   medications. And so I think that monitoring for

8   hemoptysis is going to be very important.

9   With that said, I think your proposed plan to

10 send questionnaires to the health care provider falls a

11 little bit short. And I think that in this electronic

12 age we really have a duty to gather all of the

13 information we can, and perhaps developing an app or

14 something like that that the parent themselves would

15 fill out on their Smartphone or tablet, so that you can

16 collect the data directly from the parent at a time

17 that is probably closer to the event occurring rather

18 than having them try and recollect and report that to

19 the PCP. And I think that the data would be more robust

20 to follow this event over the long term.

21   DR. FOX: Okay. Thank you for that comment.

22 So it's something we could discuss with the FDA, though

1 I think one of the great things about the CFF database

2 now is actually collecting data on every visit, whereas

3 in the past it has been sort of on an annual sort of

4 count basis, now the data is being collected per visit.

5 So I think the CFF database is a very rich source for

6 that.

7   DR. JACOBY: Okay. Thank you, everybody.

8 Thank you for your presentations and the questions from

9 the Committee. We are going to take a 10-minute break.

10 We will be back at 10:48.

11   (A break was taken.)

12   DR. JACOBY: We are going to have the

13 presentations by the FDA now, and there will be an

14 opportunity for questions and clarifications after

15 that.

16   Before we get into that, just in the interest

17 of moving things along, I am going to introduce what I

18 would call an anti-filibuster rule. I think that

19 everyone's questions were very well thought out and all

20 of the discussion was very important.

21   I would encourage the Committee members to

22 think of the one most important question that you want

1 to ask and ask that question and let's -- just in the

2 interest of being able to get through the presentations

3 and have one everyone represented. And I will

4 apologize in advance if I have to cut anyone off. My

5 decisions on cutting people off will be arbitrary,

6 capricious, and final. So -- (Laughter.) FDA

7 Presentations

8   DR. WITZMANN: Good morning. My name is

9 Kimberly Witzmann, and I'm a medical officer in the FDA

10 in the Division of Pulmonary, Allergy, and Rheumatology

11 Products. I am a pediatric pulmonologist by training,

12 and before coming to FDA I spent a decade working with

13 CF patients and their families at an accredited CF

14 center.

15   I would like to thank Dr. Jacoby and the

16 members of the Pulmonary Advisory Committee for being

17 here to share your expertise, and to thank the CF

18 community for their involvement and participation in

19 these clinical trials.

20   Over the next 75 minutes, members of the FDA

21 will review data from the new drug application for

22 mannitol inhalation powder, which we will refer to as

 1 dry powder mannitol or DPM throughout the course of our

 2 presentation.

 3   I will begin by providing a brief overview of

 4 the DPM clinical program. This will be followed by a

 5 statistical review of efficacy by Ms. Feng Zhou and Dr.

 6 Thomas Permutt. I will then return to the podium to

 7 provide a clinical review of the efficacy and safety

 8 data which will form the framework for the risk/benefit

 9 profile of the proposed product.

10   I will now begin the overview of the clinical

11 program. Overview of the Clinical Program

12   DR. WITZMANN: We all agree that cystic

13 fibrosis is a serious disease marked by significant

14 morbidity and early mortality. As you have heard

15 described in the sponsor and FDA presentations, there

16 is no cure for CF, and with the exception of a recently

17 approved therapy to treat a subgroup of patients, all

18 drugs available for CF treat the symptoms and sequelae

19 of disease.

20   This table lists some of the more commonly

21 used respiratory treatments for CF, both for FDA

22 approved indications and those with common off-label

1 usage.

2   Bronchial clearance of secretions is critical

3 for most CF patients. This can consist of a complex

4 regimen of chest physiotherapy, positive expiratory

5 pressure generation, inhaled bronchodilators, and

6 inhaled agents used as mucolytics, such as DNase or

7 hypertonic saline or both. The drug we will discuss

8 today is another such inhaled agent.

9   The subject of today's discussion is dry

10 powder mannitol or DPM. It has been referred to as

11 mannitol inhalation powder in the literature and is

12 known in the CF community by its proposed trade name,

13 bronchitol.

14   A related product is marketed by the same

15 sponsor under the trade name aridol test kit, which is

16 used in the assessment of bronchial

17 hyperresponsiveness. Like methacholine, aridol is

18 labeled with a box warning for its risk of causing

19 severe bronchoconstriction.

20   As you have heard, the proposed indication

21 for DPM is for the management of cystic fibrosis in

22 patients age six years and older to improve pulmonary

1 function. And the proposed dose is 400 milligrams twice

2 daily, which consists of inhaling the contents of 10

3 capsules twice a day administered with a dry powder

4 inhaler device.

5   Here is a brief outline of the regulatory

6 history for DPM for the CF indication. The

7 investigational new drug application was opened on

8 November 22, 2004. It was granted orphan drug status

9 in

10   2005 and fast-track development status in

11 2006. During the end of Phase II meeting on February

12 15, 2006, key discussion topics with the sponsor

13 included the following: that Phase III study duration

14 would differ depending on primary outcome measure

15 chosen. For example, a six-month study duration would

16 be reasonable for FEV1 outcome, but that one-year

17 duration would be needed for an exacerbation endpoint;

18 that one-year safety data was necessary for

19 registration because of proposed chronic use for the

20 product; and that a variety of proposed endpoints may

21 or may not be suitable.

22   Specifically, the choice of an FEV1 variable

1 would be reasonable, but because bronchitol is not

2 expected to act as a bronchodilator, small changes in

3 FEV1 over short periods of time would not, by

4 themselves, be sufficient to support approval, and

5 additional co- primary or secondary outcomes would be

6 required.

7   A pre-NDA meeting was held on December 10,

8 2010, during which time the sponsor presented their

9 proposal for post-hoc changes to the statistical

10 analyses. We acknowledged the sponsor's use of post-hoc

11 analyses, but noted that it was premature for us to

12 comment on the adequacy of such as this would be part

13 of the NDA review.

14   We were clear to state that such analyses are

15 generally considered hypothesis-generating or

16 exploratory, and typically require confirmatory

17 studies. Ms. Zhou will discuss these statistical issues

18 later in her presentation.

19   The sponsor's development program has been

20 described in detail, so my overview will be brief. As

21 you recall, the program consisted of seven studies.

22 They included two Phase III trials already described by

1 the sponsor, and the other five studies were from the

2 early development program. All but one of these

3 studies were open label.

4   The DPM development program had a single dose

5 ranging study. Study 202 was conducted at 12 sites in

6 Canada and Argentina. Eighty-five CF patients age

7 seven years and older with FEV1 of 40 to 90 percent

8 predicted were initially evaluated. Because inhaled

9 mannitol has the known risk of causing severe

10 bronchoconstriction, the first challenge dose, called

11 the mannitol tolerance test, or MTT, was given to each

12 patient in a controlled setting at visit one.

13   After exclusion for positive test or other

14 reasons, 48 patients remained in the evaluable

15 population. In the first treatment period, all patients

16 received 400 milligrams twice daily dose of DPM for a

17 two-week course, followed by a one-week washout period.

18 They then began randomized enrollment into each arm of

19 40, 120, or 240 milligrams DPM twice daily for two

20 weeks, with one-week washouts between each.

21   Forty-four patients completed the study,

22 having received two weeks' treatment at each dose of

1 DPM, and 38 patients met the per-protocol definition

2 with no missing data.

3   Although the design of Study 202 was

4 problematic, since all patients began their treatment

5 sequence with the 400 milligram twice a day arm,

6 followed by randomized treatment periods with the three

7 lower doses, a dose-response was observed.

8   This graph shows the FDA's analysis of

9 percent change from baseline in FEV1 at the end of each

10 treatment period for Study 202. It demonstrates that

11 the 400 milligram dose of DPM provided the greatest

12 change in FEV1 with no marked change seen at the 40

13 milligram dose of DPM. In fact, treatment with the 40

14 milligram dose demonstrated a negative change of 1.57

15 percent. Four hundred milligrams was the highest dose

16 of DPM evaluated.

17   Based on the lack of response at the 40

18 milligram dose in Study 202, and the need to account

19 for the sweet taste of mannitol for blinding purposes,

20 a 50 milligram dose was selected as a control for the

21 Phase III studies.

22   The focus of the FDA efficacy presentation

1 will be the two Phase III trials in CF which utilize

2 the proposed dosing regimen under review. Studies 301

3 and 302 were conducted sequentially. They were both

4 randomized, double-blinded, controlled, parallel group

5 studies of 26 weeks' duration comparing the 400

6 milligram dose of DPM to a 50 milligram control dose.

7   For the remainder of the FDA presentation,

8 the 400 milligram active dose will be referred to as

9 DPM, and the 50 milligram dose will be called

10 "control."

11   Study 301 included 295 patients from 40 sites

12 in Australia, New Zealand, the United Kingdom, and

13 Ireland, of whom 177 received DPM and 118 received

14 control. Study 302 included 305 patients from 53 sites

15 in the U.S., Canada, Argentina, and Europe, of whom 184

16 received DPM and 121 received control.

17   For both studies, the primary efficacy

18 endpoint was change in absolute FEV1 across 26 weeks.

19   The design of both studies was very similar.

20 Due to the known bronchoconstrictive properties of

21 mannitol, a mannitol tolerance test or MTT was given to

22 each patient in a controlled setting at the screening

1 visit. Patients not failing the MTT would progress to

2 visit one, at which time they were randomized to

3 receive DPM or control in a three-to-two fashion.

4 Patients were evaluated at weeks six, 14, and 26.

5   Study 302 included two 26-week open-label

6 extensions, and Study 302 had one.

7   Pertinent enrollment criteria for both

8 studies were comparable. Inclusion criteria were

9 similar, with the exception of a difference in the

10 lower border of allowable percent predicted FEV1 at

11 baseline, 30 percent for Study 301, and 40 percent for

12 Study 302.

13   Exclusion criteria for both studies include

14 those patients with a history of significant hemoptysis

15 and use of hypertonic saline. Hemoptysis will be

16 discussed further in our safety presentation.

17   A total of 731 patients were enrolled for

18 these two studies for the combined population; 719

19 patients were evaluated for bronchospasm at the

20 screening visit using the MTT. Forty-one patients were

21 test positive, and an additional 27 patients were not

22 able to complete the MTT testing procedure, with 68

1 total, or 10 percent, who could not tolerate a single

2 administration of DPM. This is similar to the dose

3 ranging Study 202, which also had a large number of

4 patients who did not pass the MTT.

5   An additional 52 patients did not receive

6 blinded study drug at visit one. Thus, out of the 731

7 patients enrolled, the ITT population included 600

8 patients or 82 percent of those evaluated. You will

9 hear about additional dropouts from the ITT population

10 in both the efficacy and safety discussions later.

11   The baseline characteristics for patients

12 across the two studies were similar and not unexpected

13 given the disease being studied. For example, the

14 average patient's age was early twenties, and over 95

15 percent of patients were Caucasian. Patients were

16 receiving standard of care therapies. The study was

17 stratified to account for the use of rhDNase, but, as

18 mentioned previously, the use of inhaled hypertonic

19 saline was prohibited.

20   Overall, the studies note a similar mean FEV1

21 and mean FEV1 percent predicted, supporting the

22 similarity of patient populations at baseline within

1 these two studies. Patients in Study 302 had a higher

2 rate of pancreatic insufficiency, and Study 301 showed

3 a slightly higher rate of patients chronically infected

4 with mucoid strains Pseudomonas aeruginosa at baseline.

5   This table lists the primary and secondary

6 endpoints for both studies. Neither study protocol had

7 pre-specified key secondary endpoints, nor a pre-

8 specified ranking of secondary endpoints. The

9 statistical analysis plan for Study 302 did specify

10 five key secondary endpoints. However, two of these

11 were not identified as endpoints in the protocol.

12   Ms. Zhou will describe these endpoints in

13 further detail in her presentation of the efficacy

14 data.

15   I will now turn my presentation over to Ms.

16 Zhou, who will discuss the efficacy analyses for this

17 program, followed by Dr. Permutt's additional

18 interpretation of the key statistical issues for this

19 application. Statistical Review of Efficacy

20   MS. ZHOU: Thank you, Dr. Witzmann. My name

21 is Feng Zhou. I am the FDA statistician responsible

22 for the primary statistical review for the application

1 for DPM for management for cystic fibrosis that we are

2 here to discuss today.

3   This talk will focus on the Phase III study

4 of DPM. I will begin with a brief description of the

5 design of the studies, focusing on the area of concern

6 to the division. Next, I will describe the

7 differential patterns of early treatment

8 discontinuation that were observed in each study.

9 Subsequently, I will describe the issues associated

10 with the implementation of the pre- specified

11 statistical model for the primary efficacy analysis in

12 the presence of the early study discontinuation.

13   I will propose and then present sensitivity

14 analysis and an additional method referred to as

15 cumulative responder analysis for summarizing the

16 primary efficacy data in the presence of missing data.

17 I will continue the presentation with the result of a

18 certain secondary efficacy endpoints, and then finish

19 with a comment regarding the efficacy of DPM in the

20 pediatric subgroup.

21   You heard the applicant's description of the

22 studies, so I will be brief. Studies 301 and 302 were

1 similar in design. They were both double-blind,

2 parallel group, randomized studies. Randomization was

3 stratified by rhDNase use in the region for the Study

4 301 and the country for Study 302.

5   Subjects were to receive either DPM or

6 control for the entire 26 weeks' double-blind treatment

7 period. Studies 301 and 302 were not conducted

8 concurrently, so that 302 was designed with experience

9 obtained during the Study 301 known.

10   The applicant had indicated that subjects in

11 the Study 302 were given more realistic expectation

12 regarding the likelihood of cough following DPM

13 administration than were the subjects in the Study 301.

14 Both studies required a negative outcome to mannitol

15 tolerance test at week two -- two to five weeks before

16 baseline for randomization. However, the method of

17 giving the test drug dose was slightly different

18 between two studies.

19   The primary efficacy endpoint in each study

20 was absolute change from baseline in FEV1 across 26-

21 week double-blind treatment period. While numerous

22 discrepancies in the statistical method proposed for

1 the quantified primary and secondary efficacy data

2 existed between the protocol and the statistical

3 analysis planned for each of the studies, the applicant

4 has indicated that finalization of the SAPs occurred

5 before unblinding.

6   The division is accepting the method

7 described in the SAP as a pre-specified method. In

8 each study, the SAP specified analysis method for the

9 primary efficacy endpoint was a mixed model for

10 repeated measurements or MMRM, with the predictors

11 listed here. The predictors differed slightly between

12 studies, but not in a way that would materially impact

13 the results we are showing you today.

14   Both SAP defined "intent-to-treat population"

15 as all subjects randomized who receive at least one

16 dose of study drug. One interim efficacy analysis was

17 conducted in each study. In other words, the DSMB was

18 to make recommendations regarding continuing or

19 stopping the study, so that to maintain overall Type 1

20 error rate of 0.05, the final two-sided significance

21 level for reference in the primary efficacy analysis is

22 0.0498.

1   For Study 301, no secondary efficacy

2 endpoints were distinguished as being a part of a pre-

3 specified multiplicity plan to control Type 1 error.

4 For Study 302, the SAP specified that a Holm's

5 procedure would be applied to the following list of key

6 secondary efficacy endpoints.

7   This slide provides description of the

8 differential early study discontinuation as well as the

9 ITT and a modified ITT population that had been

10 utilized in the efficacy analysis. We begin with the

11 ITT group shown in a table in blue text.

12   From here, early study dropout was noted

13 before the first post-baseline measurement at week six,

14 occurring more frequently in the DPM group than the

15 control group. In Study 301, 20 DPM and six control

16 patients withdrew without providing any post-baseline

17 data. In Study 302, seven DPM and the one control

18 patient withdrew without providing any post-baseline data.

19   These withdrawals are likely treatment-

20 related. However, because these patients have not

21 reported any post-baseline measurements, these patients

22 are completely excluded from many of efficacy analysis.

1   The remaining patients formed the modified ITT or MITT

2   population shown here with red text.

3   Analysis utilizing the MITT population could

4   be biased by exclusion of these subjects. In

5   considering the various efficacy analysis, clear

6   specification of the -- whether the ITT or MITT

7   population has been analyzed is needed for the full

8   understanding of the result.

9   Differential early discontinuation continued

10 throughout the treatment period, so that 64 percent of

11 DPM and 73 percent control patients in Study 301, and

12 83 percent of DPM and 88 percent of control patient in

13 Study 302, complete the intended 26-week treatment period.

14   These completion rates are in the purple text

15 in the table and illustrate the discontinuation that

16 occurred during Studies 301 and 302. The

17 discontinuation rates were differential by treatment

18 group in both studies, but more prominently so in Study

19 301. Overall, the most common reasons for early study

20 discontinuation were withdrawal by patient and adverse

21 event.

22   In order to carry out statistical analysis

1 utilizing either the MITT or ITT population,

2 assumptions regarding this differentially missing data

3 will need to be made. If these assumptions are not

4 reflective of the true nature of this data, if this has

5 been observed, the treatment effect estimates resulting

6 from this analysis may be inaccurate.

7   This table shows the result from the SAP pre-

8 specified MMRM model for each study. The average

9 difference between treatment groups in the change from

10 baseline in FEV1 was 83 mL in Study 301 and 54 mL in

11 Study 302. In Study 301, this difference is

12 statistically significant with the lower limit of the

13 95 percent confidence interval, demonstrating that the

14 average result was that DPM should be expected to be at

15 least a 39 mL greater than that of the control group.

16   In Study 302, the difference between

17 treatment groups of 54 mL is not statistically

18 significant. Highlighting the lower limit of 95 percent

19 confidence interval for the difference between the

20 treatment group we see that this analysis suggests that

21 mean difference between treatment group could be less

22 than zero at the negative two mL.

 1   However, this analysis may be being

 2 influenced by the differentially missing data

 3 previously described. First, this analysis utilized the

 4 MITT population, not the ITT population, and,

 5 therefore, are impacted by the exclusion of a subject

 6 without the post-baseline data.

 7   It is difficult to quantify the impact that

 8 this subject exclusion may have had on the overall

 9 estimate of the average treatment effect, but there is

10 potential that estimate of the treatment effect being

11 shown here is exaggerated.

12   Secondly, the subjects with some but not

13 completed post -- FEV1 data are included in the MMRM

14 analysis by requiring an assumption that the missing

15 data been missing at the random, meaning the early

16 discontinuation rates are not the same in both

17 treatment groups for either study. And the nature of

18 the reason for withdrawal suggests that early study

19 withdrawal is associated with coughing.

20   The missing data likely did not occur at the

21 random, but are directly linked to the treatment

22 assignment, so that the statistical assumptions require

 1 that the missing data is missing at the random is not

 2 justified.

 3   In summary, the frequency and

 4 disproportionate early subject discontinuation rate in

 5 these studies, particularly in the Study 301, raises

 6 serious statistical concern regarding its accuracy of

 7 treatment effect resulting from the pre-specified of

 8 MMRM primary efficacy analysis.

 9   Many sensitivity analyses were untaken with

10 the goal of understanding the impact of missing data

11 had on the pre-specified primary efficacy analysis.

12 Some of the analyses have been presented by you -- to

13 you by applicant. As you may guess, some results are

14 better than others, but none of them are perfect.

15   While description of the sensitivity analysis

16 may at first make them seem conservative, even

17 punitive, close examination of assumptions underlying

18 several of this method review that this method relied

19 heavily on the missing data at random assumptions.

20 These methods, therefore, more or less impute the

21 missing data by preserving the treatment effect that

22 was observed prior to the discontinuation, even though

1 DPM patient who had dropped -- have dropped out are no

2 longer taking the drug.

3   A sensitivity analysis that does not have

4 this fault is the baseline observation carried forward

5 or BOCF approach. However, BOCF also is not perfect,

6 because a single value is imputed for all missing data.

7 The variance may be being underestimated.

8   The assumption that while we agree with the

9 criticism of the method that the BOCF analysis may

10 overstate the statistical significance of the result

11 slightly, we also believe BOCF provides a conservative

12 estimate of the point estimate of treatment effect in

13 the setting of the missing data such as is observed in

14 this study.

15   In Study 301, the difference between DPM and

16 the control in the change from based on FEV1 is

17 estimated to be 62 mL. This is supportive of the

18 conclusion from the pre-specified primary analysis that

19 DPM is having more of the effect than control. But it

20 suggests that a difference between the treatment group

21 is smaller than the point estimate of 83 mL observed in

22 the pre-specified analysis.

1   In Study 302, this difference is estimated to

2 be 65 mL, and it's fairly consistent with the pre-

3 specified analysis. To supplement and the pre-

4 specified and BOCF analysis, next I will present an

5 additional method for summarizing the primary efficacy

6 data that accounts for the missing data by considering

7 subject with the missing data as a non-responder.

8   This slide shows the post-hoc analysis of the

9 primary efficacy endpoint, which is referred to as a

10 continuous response plot. This analysis is desirable

11 because in this analysis all patients who discontinued

12 the study early are considered in non-responder. We

13 believe this is appropriate characterization of the

14 performance of study treatment, and that if a subject

15 is not willing to continue taking the medication, no

16 efficacy can be expected to be gained from the product.

17   In this plot, the horizontal X-axis displays

18 the threshold required to classify a patient as a

19 responder. This vertical Y-axis presents the proportion

20 of ITT patients who achieved the corresponding

21 threshold. The proportion of DPM responders is

22 represented by the red line and the proportion of a

1 control responder by the blue.

2   Interpreting these figures we first note that

3 the curve showed initial dramatic drop from 100 percent

4 to approximately 60 percent to 75 percent in the Y-

5 axis. This corresponds to the proportion of the patient

6 who discontinued the study early, since the patients

7 with the missing data were classified as non-responder

8 for all thresholds.

9   Moving towards the right of the figure in

10 each study there is some separation between the

11 treatment groups with the DPM group having numerically

12 higher proportion of patients who achieved an increased

13 change from baseline in FEV1 threshold than does the

14 control group. This is evident by the fact that the

15 red line generally lies above the blue line in those

16 figures.

17   On the next slides, we will provide test for

18 the difference between the treatment group in this

19 curve at several special thresholds.

20   This table provides a comparison of the

21 proportion of DPM and the control subject who achieved

22 at least a 50, 75, or 100 mL change in FEV1 from

1 baseline to week 26. The entire ITT population is

2 included in this analysis. Patients with the missing

3 data are classified as a non-responder for this

4 analysis. For Study 301, there was no statistically

5 significant difference between treatment groups in the

6 proportion of DPM responder compared to that of the

7 control patients. However, numerical trends that

8 favored DPM over control were present at each threshold

9 examined.

10   These numerical trends are consistent with

11 the indication from the MMRM analysis that DPM have

12 provided a beneficial effect on the primary efficacy

13 and endpoint as compared to control.

14   For Study 302, the differences between the

15 treatment groups and the proportion of the subject who

16 achieved each threshold examined were higher in the DPM

17 group than control group. This is supportive of the

18 suggestion of the beneficial effect of DPM relative to

19 control on the primary efficacy endpoint.

20   Both MMRM and responder analysis will be

21 discussed further in a few minutes by Dr. Permutt.

22   I am now moving to the presentation of the

1 selected secondary efficacy endpoints. The conclusion

2 regarding treatment effect on the spirometry-related

3 endpoints generally would be expected to be similar to

4 that of the primary efficacy endpoint. They examined

5 the effect on the DPM outside that of the spirometry-

6 related endpoint. The following endpoints were

7 selected by FDA clinical team, and they were presented

8 here -- pulmonary exacerbation, rescue antibiotic use,

9 hospitalization, and a quality of life measure.

10   By treatment group, comparison of the rate of

11 the pulmonary exacerbation is provided in this table.

12 This analysis includes the entire ITT population.

13 However, the result may have been impacted by the

14 differential early study discontinuation in that

15 patients who are not participating in the study are not

16 available to report occurrence of the event.

17   While this analysis is to adjust for the

18 differential exposure time, the also missing data

19 would have been missed similar to observed data if they

20 had been observed, which may not be a realistic

21 assumption. Regardless, no statistical significant

22 difference between the treatment group in the rate of

1 exacerbation were observed in the NDA study.

2   The applicant had highlighted this data,

3 saying that the numerical trends are supportive for the

4 treatment of DPM. However, even the numerical trend

5 may be artificially inflated because the differential

6 missing data. This is especially the case for Study

7 301.

8   Similar results were observed for the rate of

9 the rescue antibiotic use episodes and the rate of

10 hospitalization due to exacerbation. No statistically

11 significant difference between treatment groups for

12 either endpoints were observed in either study.

13   Quality of life was a measure used the

14 quality of life respiratory domain from the cystic

15 fibrosis questionnaire. For this endpoint, the pre-

16 specified analysis difference between studies. For the

17 Study 301, the pre-specified method was the MMRM model

18 estimating overall effect across 26-week treatment

19 period. For Study 302, the SAP specified that effect

20 would be estimated at the week 26 using ANCOVA model

21 and LOCF imputation method. No statistically

22 significant difference between treatment groups in the

1 quality of life were observed in either study.

2   I am moving now to the subgroup analysis of a

3 primary efficacy endpoint by age group. Because of the

4 differential early study discontinuation, and the

5 descriptive nature of subgroup analysis in general, the

6 cumulative responder plot are being employed here.

7   This slide shows result for Study 301 on the

8 left is cumulative respond plot for the six to 17 years

9 age group. On the right is the same for the 18 and

10 older group. There was about 100 patients age six to

11 17 years old, and 200 patients were 18 and older. For

12 this study, we note that numerical difference between

13 the proportion of DPM responders and that of the

14 control subjects appear to be smaller in the younger

15 age group than the adult group.

16   For example, at the threshold of the 100 mL,

17 the numerical difference between treatment groups in

18 the proportion of a successful treatment with DPM and

19 the control subjects is zero percent in the six- to 17-

20 years- old subjects, while it is 11 percent in the 18

21 and older subjects.

22   This is unknown whether this numerical

1 difference in the treatment effects, besides the

2 difference in two age groups in Study 301, represent a

3 real difference in the performance of a DPM by age

4 group or merely random variation.

5   Study 302 suggests a different conclusion

6 regarding the effect of the DPM in pediatric as

7 compared to adult. The numeric -- number of the

8 patient were evenly distributed in the two age groups.

9 The treatment difference in adult and the pediatric was

10 similar in both age groups.

11   In summary, the overriding statistical

12 concern in the analysis of efficacy data in Studies 301

13 and 302 is the treatment-related or frequent early

14 study discontinuations. This is more problematic in

15 the Study 301 than the Study 302. In Study 301, 64

16 percent of DPM and 73 percent of control subjects

17 completed the 26-week treatment period.

18   In Study 302, the 83 percent of DPM and 88

19 percent of the control subjects completed a 26-week

20 treatment period. The MMRM estimates of the treatment

21 effect using the continuous change from baseline and

22 FEV1 outcome may not be accurate, because the

1 differential effect this early study withdrawal may

2 have been had.

3   BOCF analysis and the continued response are

4 numerically consistent with a positive treatment effect

5 for DPM related to the control. But for the Study 301,

6 this analysis suggests that the magnitude of the

7 treatment effect size may be smaller than the 83 mL

8 estimated by the pre-specified analysis.

9   To summarize the conclusion regarding the

10 secondary efficacy endpoints, no statistical significant

11 difference between treatment groups were demonstrated

12 for any non-spirometry endpoint. This statement may

13 seem in conflict with some material regarding the

14 secondary efficacy endpoint that is included in the

15 applicant's briefing package as well as their

16 presentation here today.

17   The major difference between the presentation

18 of a secondary endpoint by the applicant as compared to

19 that by the FDA is that the applicant is frequently

20 highlighting the numerical difference without reference

21 to their lack of statistical significance.

22   Finally, in Study 301, numerical difference

1 between the treatment group in the cumulative response

2 plot for the primary efficacy endpoint appear to be

3 smaller in the age six to 17 group compared that in the

4 age 18 and above. This type of difference in the

5 treatment effect between the age groups was not

6 observed in Study 302.

7   Next, I would like to introduce Dr. Permutt.

8 Dr. Permutt will comment further on both the pre-

9 specified and the sensitivity analysis used to quantify

10 the primary efficacy endpoint.

11   Thank you.

12   DR. PERMUTT: I'm Tom Permutt. I supervise

13 the statisticians who have primarily reviewed this

14 product. Because the statistical issues here are

15 crucial to understanding the effect of the drug, and

16 especially because they turn on problems of missing

17 data, which are a special interest of mine, I think it

18 is appropriate for me to give you my perspective on the

19 results.

20   FDA statisticians usually lay heavy stress on

21 the pre-specified primary analysis. We haven't here,

22 and I want to talk about why and about what we've done

1 instead. We also often like to focus on analysis of

2 all patients treated regardless of adherence, and I'll

3 talk about how this case might be a little different.

4   I'll tell you about the role played by

5 sensitivity analysis in persuading us that the product

6 has an effect on FEV1, and I will -- at least in Study

7 301, and I will show you how I think that effect should

8 be described.

9   The pre-specified primary analysis, as you

10 have heard, used a mixed model for repeated measures.

11 That's a precise but somewhat obscure and somewhat

12 ambiguous way of describing what was done. In fact,

13 the analysis amounts approximately to calculating the

14 average across time of the available observations for

15 each patient and then a t-test comparing a means for

16 the two groups.

17   It is a good statistical method for answering

18 a different question than the one I think is important

19 here. In particular, it may be an excellent method in

20 cases where subjects are lost to followup and you don't

21 know what happened to them, and you want to estimate

22 what happened to them as best you can from what you

1   know about patients who were not lost to followup.

2   That is not what we have here. We have a

3   substantial minority of patients who were unable to

4   tolerate the treatment. We know what happened to them.

5   They stopped taking it. It would not be reasonable to

6   think their outcomes were like the patients' and people

7   who continued taking it.

8   More specifically, a patient who tolerates

9   the drug up to, say, the first visit and has improved

10 pulmonary function at that visit, and then has to

11 discontinue, contributes good score to the analysis,

12 but such a patient has not had a good outcome.

13   Okay. But most patients did tolerate the

14 treatment. We can ask, as some people have suggested

15 earlier this morning, how much their pulmonary -- we

16 can ask how much the pulmonary function improved in the

17 tolerators. Is this what we want to know here? Well,

18 actually, I think it might be. This is not like, say,

19 chemotherapy where everybody gets treated, everybody

20 suffers toxicity, and the primary question about

21 outcome just has to be, how did everybody do?

22   Here people who don't tolerate the treatment

1 stop taking it. They may not have been harmed much.

2 And I think you can make a strong argument that what

3 you would most like to know is what happens to people

4 who do take it. Unfortunately, that is not at all easy

5 to estimate.

6   The obvious thing, as, for example, Dr. Flume

7 suggested, is to look at the people in the active group

8 who did in fact complete the course of treatment.

9 Well, so far so good. The trouble is, compared to

10 whom? You would need to compare them to people like

11 them in the control group, but you can't tell who in

12 the control group are like them in the relevant way,

13 which is that they would have tolerated the active

14 treatment.

15   Unfortunately, even what are here called

16 intent to treat analyses, as you have heard, suffer

17 from the same defect because early dropouts are

18 excluded. So, in this case, the pre-specified analysis

19 on its own is not altogether persuasive to us, and

20 there is no simple fix. We've seen a lot of alternative

21 analyses presented both by the applicant, by Ms. Zhou.

22   Many of them suffer from the same basic

1 defect as the primary analysis in that they effectively

2 assign good scores for patients who improve and then

3 discontinue.

4   This slide doesn't represent data, but it is

5 meant to show schematically what the various

6 sensitivity analyses do with a patient who does well at

7 the first visit and then drops out. And I can be brief

8 here because Dr. Herring has already made these points

9 rather eloquently, but let me try to reinforce them a

10 little bit.

11   Very broadly, there are two kinds of analysis

12 shown here, one in green and the rest in not green. So

13 look at the solid lines, which represent a hypothetical

14 patient in the active treatment group. He gets better

15 and then drops out. The three top lines are all

16 different methods represented in the sensitivity

17 analyses, but they all impute, on average, an improved

18 score to this patient.

19   The green line represents a return to

20 baseline. As a primary analysis, as you've heard,

21 baseline imputation has been rightly criticized with

22 imputing what may sometimes be an unrealistically bad

1   score, and as well because of the problem of

2   variability. The green line does not bounce around.

3   The top three solid lines bounce around from visit to

4   visit, both systematically with the -- as the average

5   scores of patients who do complete vary across visits

6   and also randomly, and we don't get that bouncing

7   around in the -- in the green baseline carried forward

8   analysis.

9   We are not too keen on it as a primary

10 analysis. What we would like to see here, as Dr.

11 Herring and the conversation that followed Dr.

12 Herring's remarks suggested, is an analysis that

13 incorporates the good feature of the other analyses in

14 terms of accounting for variability with the good

15 feature of baseline that it does not impute a benefit

16 to patients who might get better for a while and then

17 drop out because, as Ms. Zhou said, we don't expect

18 those patients to be benefitting from treatment in the

19 long term.

20   So we don't have an analysis just like that

21 to show you. We are confident that the sensitivity

22 analyses taken as a whole support the primary analysis

1 in Study 301 and rule out the possibility that the

2 positive result is attributable solely to the way

3 missing data were handled.

4   We do think the effect on FEV1, though non-

5 zero, is probably somewhat overstated by the primary

6 analysis. Smaller values around 50 or 60 milliliters,

7 rather than 80, seen in some other analyses of Study

8 301, as well as in Study 302, are more realistic.

9   Besides the mean effect, another way to

10 describe the effect on FEV1 is by carefully

11 interpreting the empirical distribution functions,

12 because that's what they are, that Ms. Zhou showed you.

13   Now, I share Dr. Fox's concern about the loss

14 of information in arbitrary dichotomies. But if you

15 consider all the possible dichotomies, you actually get

16 all of the information back. And, besides, once you

17 have convinced yourself that there is an effect, if you

18 do convince yourself of that, I think it is -- these

19 curves are a very useful way of looking at what that

20 effect is.

21   So let me remind you about how this graph was

22 constructed. All patients randomized are shown here.

1 Dropouts are shown on the left side, and what the left

2 part of the curve looks like depends a lot on what

3 assumptions you make about dropouts, but that's not so

4 for the right side of the curve.

5   So, for example, if you look where we have

6 drawn the vertical reference line at 100 milliliters,

7 about 35 percent of patients on active drug, about 28

8 percent of papers on control, had such an improvement,

9 an improvement of 100 milliliters or better.

10   It is a difference of about seven percent.

11 Another way of saying that is for every 100 patients

12 treated, seven might have an improvement of that

13 magnitude attributable to the drug. We don't focus

14 exclusively on 100 milliliters, of course. You can see

15 more or less similar results at 50 or 200 or other

16 values. There is uncertainty, which is difficult to

17 portray in this kind of graph.

18   Again, there is little enough uncertainty

19 that we are reasonably confident the effect is in the

20 right direction. But it could be numerically

21 substantially more or less than we are seeing.

22   Study 302, you see rather different-looking

1 curves, and the applicant and the FDA are agreed that

2 the results in Study 302 should not be taken as

3 statistically significant. They don't so much

4 contradict the results of Study 301 as lend it very

5 weak support.

6   They tell a fairly similar story.

7 Improvements in FEV1 of 50 or 100 milliliters were seen

8 in a substantial minority of patients on control, and

9 in a slightly larger minority on active drug.

10   Thank you for your attention. Clinical Review

11 of Efficacy, Safety, and Risk/Benefit

12   DR. WITZMANN: Thank you. I will deliver the

13 last presentation for the FDA this morning.

14   Here is the outline for this portion of my

15 presentation. I will begin by discussing the clinical

16 implications of the efficacy data, which you have just

17 heard presented by the FDA statistical team, with the

18 goal of providing contacts for the clinical

19 interpretation of this data.

20   Next, I will review safety data with a

21 presentation of the main safety results including non-

22 fatal serious adverse events, withdrawals due to

1 adverse events, and common adverse events, with a focus

2 on some specific safety concerns and safety for the

3 subgroup of pediatric patients.

4   Finally, I will conclude by providing a

5 framework for discussion of the risk/benefit profile

6 for DPM.

7   So, to begin, let me summarize the efficacy

8 findings for DPM in CF. In the sponsor's primary

9 efficacy analysis submitted to the NDA utilizing the

10 MMRM in the modified ITT population, which does not

11 include data from those patients who dropped out before

12 week six.

13   Study 301 shows the statistically significant

14 improvement in FEV1, but Study 302 does not. Most of

15 the sponsor's sensitivity analyses provide support to the

16 significance in Study 301, as you have seen in previous

17 presentations.

18   The second portion of this table lists an

19 additional sensitivity analysis conducted by FDA, the

20 baseline observation carried forward analysis, for the

21 full ITT population. For Study 301, it, too, made

22 statistical significance with 95 percent confidence

1 intervals from 15 to 107 milliliters.

2   So the results of this additional analysis

3 remain consistent with the results achieved in the

4 sponsor's primary analysis of Study 301 and supports

5 the idea that the positive result for Study 301 was not

6 due solely to the way missing data were handled.

7   Note that the result for Study 302 continues

8 to not meet statistical significance for this baseline

9 observation carried forward sensitivity analysis.

10   So how do we interpret this data? We need to

11 examine how we think of FEV1 as an endpoint for CF in

12 the context of drug development. First, inhaled

13 mannitol is not a bronchodilator, but, rather, it

14 facilities airway clearance. Therefore, the change we

15 would expect with chronic use should result in improved

16 pulmonary outcomes.

17   In this case, FEV1 is being used as a measure

18 for overall improvement in pulmonary function. In the

19 context of cystic fibrosis, we would expect that

20 meaningful improvement should carry over to other non-

21 spirometric endpoints that better reflect overall

22 pulmonary function, such as fewer infections,

1 hospitalizations, and exacerbations and a better

2 quality of life.

3   So if DPM were having significant impact upon

4 overall pulmonary function, we would expect to see

5 support from clinically meaningful secondary endpoints

6 chosen in these studies. In this light, Studies 301

7 and 302 showed numerically positive trends but no

8 statistically significant changes in any of the chosen

9 secondary endpoints, including incidence of or time to

10 first pulmonary exacerbation, rescue antibiotic use,

11 days in the hospital due to exacerbation, or quality of

12 life scores.

13   It is important to note that the 26-week

14 timeframe is not significant, is not substantial enough

15 to truly measure exacerbation changes as we previously

16 mentioned. It is also possible that the small change

17 in absolute FEV1 seen is too small to impact more

18 clinically meaningful outcomes in a 26-week study

19 period as we had discussed with the sponsor at the end

20 of Phase II meeting.

21   Next, I would like to examine efficacy in the

22 pediatric population. This is important because the

1 proposed indication is for patients six years and

2 older, and 43 percent of the ITT population was less

3 than 18 years of age.

4   You saw from the FEV1 changes in the

5 sponsor's pooled study data in the forest plots that

6 for pediatrics the 95 percent confidence intervals

7 crossed zero. Ms. Zhou has shown you these cumulative

8 responder plots for pediatric patients six to 17 years

9 of age based on the ITT population for both Studies 301

10 and 302.

11   The graph for Study 301 is on the left and

12 302 is on the right. To orient you, the X-axis shows

13 the specific thresholds for change from baseline FEV1

14 with the greater than or equal to 100 milliliter

15 vertical demarcation as a reference. The Y-axis is the

16 percentage of patients who met each cutoff, with DPM

17 line in red and the control line in blue.

18   For Study 301, the numerical difference

19 between the proportion of DPM subjects achieving the

20 various thresholds and the primary efficacy endpoint,

21 as demonstrated by the red line, and that of control

22 subjects in blue, shows little separation of the

1 curves, suggesting a lack of effect for pediatric

2 patients in the study.

3   Study 302 suggests a different conclusion

4 regarding the effect of DPM in pediatrics with results

5 similar to that seen both in adults and the ITT

6 population as a whole. So Study 301, which

7 demonstrates significant -- excuse me, statistical

8 significance overall, does not show separation between

9 treatment groups for the six- to 17-year-old

10 population, raising the question of the degree to which

11 we can clinically feel comfortable that the benefits

12 seen overall in 301 extends to the pediatric group.

13   We will ask you to discuss this efficacy, in

14 addition to the pediatric safety information to follow,

15 when you discuss the risk/benefit profile of DPM for

16 the pediatric population.

17   So let's review and place into clinical

18 context what we know for these two studies. First,

19 Study 301 has significant and differential dropout with

20 36 percent of the DPM and 27 percent of control

21 patients withdrawing before the end of the 26-week,

22 double-blinded period. This primary analysis does meet

1 statistical significance, and the sensitivity analyses

2 provide evidence that the effect seen is not due to

3 chance alone.

4   The point estimates from sensitivity analyses

5 range from 59 to 83 mLs, as you saw in Ms. Zhou's

6 presentation. However, when looking at the 95 percent

7 confidence intervals, the treatment effect could be as

8 small as 15 milliliters. An additional complication is

9 that the differential dropout creates two different

10 groups which we are trying to compare to one another to

11 determine the treatment effect, the DPM group of

12 tolerators as compared to a group of patients on

13 control who may or may not tolerate DPM chronically.

14   Because of this apples-to-oranges comparison,

15 we lose the ability to assess the magnitude of change

16 in FEV1 across the treatment versus control groups of

17 the CF population originally selected for

18 randomization. For regulatory purposes on which to

19 base drug approval, we typically need a comparison in

20 the same population -- in this case, DPM chronic

21 tolerators -- to determine a treatment effect.

22   For Study 302, missing data was not as

1 problematic. However, Study 302 failed to meet the

2 usual standard for statistical significance with a P

3 value of 0.059. Sensitivity analyses for this study

4 have FEV1 point estimates in the range of 49 to 63 mLs.

5   Because of a small change in FEV1 and

6 statistical significance being achieved in only one

7 study, it is important to look to other clinically

8 meaningful secondary outcomes to support FEV1 as we

9 previously told the sponsor. In this case, we see that

10 sometimes these secondary endpoints numerically favor

11 DPM, but none reach statistical significance. As such,

12 the secondary endpoints provide limited support to

13 reassure us that the small change in FEV1 is

14 representative of any other clinically meaningful

15 pulmonary improvement.

16   Last, when we examine the pediatric efficacy

17 data which was presented by Ms. Zhou in the statistical

18 discussion, there appears to be variability between

19 results from each study, with 301 suggesting a lack of

20 benefit while data from 302 suggests benefit in FEV1

21 similar to the overall study population.

22   When taken into context of the risk profile

1 for DPM, a relative lack of efficacy in pediatric

2 patients would be concerning. These are all clinical

3 issues we would like for you on the Committee to

4 explore further in your discussions of the efficacy of

5 DPM.

6   Now, I will move on to the review of safety

7 for DPM. Overall, the exposure to 400 milligrams twice

8 daily of DPM shown here is reasonable for an orphan

9 disease and meets the regulatory safety guidance

10 recommendations for a product to be administered

11 chronically to patients.

12   This slide demonstrates the major safety

13 findings for the combined safety set, which includes

14 the 26-week, double-blinded periods of Studies 301 and

15 302. There were no deaths for any patient actively

16 receiving study drug. The percentage of patients with

17 at least one serious adverse event numerically favors

18 DPM, and the number of subjects with at least one

19 adverse event is very similar between groups, also

20 favoring DPM.

21   However, the number of patients who

22 discontinued for any reason, and number of patients who

1 discontinued due to an adverse event, is higher in the

2 DPM group. We will explore these categories further.

3   It is also important to note that

4 discontinuation for any reason includes the category of

5 patient withdrawal, which meant that the patient was

6 able to withdraw from the study without clarifying

7 additional reason for why they did so.

8   This table demonstrates all serious adverse

9 events that occurred in more than two patients in the

10 safety population during the double-blind period. So

11 all preferred terms do not equal the totals shown on

12 the system organ class lines.

13   The most frequent serious adverse event in

14 both groups was for CF pulmonary exacerbation, coded as

15 condition aggravated, with 17 percent reported in the

16 DPM group and 19 percent in control group. The second

17 most common event for the treatment group was

18 hemoptysis, with a higher rate of occurrence in the DPM

19 group at eight or 2.2 percent versus two patients or

20 0.8 percent for the control group.

21   Remember that this was in a group of patients

22 who had not experienced any significant bleeding in the

1 three months prior to screening. Lower respiratory

2 tract infections did not occur at a higher rate in DPM

3 versus control.

4   This table lists discontinuations due to

5 adverse events that occurred in more than two patients

6 in the safety population during the double-blinded

7 period. A total of 41 or 11 percent of patients from

8 the DPM group, and 15 or six percent from the control

9 group, withdrew from trials due to adverse events.

10 Almost twice as many in the treatment group

11 discontinued as those who received control.

12   Most of the discontinuations in the DPM group

13 were from adverse events likely to be associated with

14 inhaled mannitol, including cough, hemoptysis,

15 bronchospasm, chest discomfort, and pharynolaryngeal

16 pain. No distinct subpopulations were

17 disproportionately represented in the dropouts.

18   Not displayed here, in the open-label phase

19 there was a higher rate of discontinuation for those

20 patients who initially received control during the

21 double-blind period, and then rolled over into open-

22 label treatment with DPM. These subjects withdrew at a

1 rate of nine percent versus two percent for those

2 continuing DPM. So chronic tolerability of DPM was an

3 issue, even in open-label observation.

4   Next, I will move on to a discussion of

5 specific safety concerns. Knowing that DPM is marked

6 as a bronchoprovocation agent, we examined the safety

7 database for episodes of bronchospasm. And because

8 hemoptysis was seen more in those receiving DPM in the

9 major safety events, it was examined more closely. So

10 these issues, in addition to overall tolerability, were

11 examined specifically for this program.

12   As you recall, 10 percent of screened

13 patients failed to complete their DPM test dose, or

14 MTT, so were not included in the intend to treat

15 population. With regard to bronchospasm episodes

16 during double-blinded treatment, you can see that there

17 is a slightly higher but not significant increase of

18 symptoms in the treatment group over control when

19 taking into consideration all adverse events that might

20 be associated with a bronchospasm. All patients were

21 pre-treated with a bronchodilator prior to study drug

22 administration.

 1   Patients with a history -- with a previous

 2 history of significant hemoptysis episode, defined as

 3 greater than 60 milliliters of blood within the three

 4 months prior to study, were excluded from the study.

 5 This table shows reported events of hemoptysis,

 6 including rates of serious adverse events, adverse

 7 events leading to withdrawal, adverse events in

 8 general, and the subgroup of adverse events classified

 9 as severe by the investigator, specifically for

10 hemoptysis.

11   While none of these occurs with high

12 frequency, the double-blind treatment period has

13 reports of hemoptysis two to three times higher in all

14 categories for the DPM treated group compared to

15 controls. This increase in hemoptysis was also seen in

16 open-label treatment. Patients who received control

17 have increased rates of hemoptysis events once

18 beginning open-label DPM that is similar to double-

19 blinded DPM treatment.

20   Those who receive DPM in the double-blinded

21 treatment period continued to have rates of hemoptysis

22 higher than the original control arm, but the rate did

1 not continue to rise with continued use. A specific

2 risk of hemoptysis in the pediatric subgroup will be

3 discussed later in this presentation.

4   This slide presents the most common adverse

5 reactions which occurred at a rate greater than four

6 percent of DPM treated patients and greater than

7 control in the Phase III double-blinded study period.

8 As you can see, the majority of events would be

9 expected with the use of inhaled DPM including cough,

10 pharyngeal irritation, hemoptysis, and vomiting.

11   There were two subgroups of patients

12 evaluated during the safety review, including pediatric

13 patients and those with severe lung disease. I will

14 show you the safety data for the pediatric population

15 in terms of overall safety, and then specifically for

16 risk of hemoptysis, in the next few slides.

17   Severe lung disease, defined by an FEV1 less

18 than or equal to 40 percent predicted, will not be

19 shown. But, in general, similar patterns were seen to

20 the overall safety population in terms of adverse

21 events, except in two important areas. First,

22 discontinuations due to adverse events occurred twice

1 as often in DPM treated patients with severe lung

2 disease than in controls. Second, adverse events of

3 hemoptysis occurred at a rate of 19 percent in DPM

4 treated patients with severe lung disease versus 10

5 percent of controls.

6   The pediatric population includes patients

7 less than 18 years old and accounts for 43 percent of

8 the total safety database, or 259 of 600 patients. In

9 general, the number of patients with any serious

10 adverse event, and with any adverse event, are both

11 lower for the DPM group.

12   However, the number of subjects with an

13 adverse event leading to discontinuation is higher in

14 the DPM group and double that of control at six percent

15 versus three percent. So we also see the effect of

16 chronic tolerability issues in the pediatric group.

17   The findings for hemoptysis were more

18 pronounced in pediatrics. As you heard in Dr. Ratjen's

19 discussion, the majority of pediatric patients have

20 lung function within the range of normal. So this is

21 especially concerning given the expectation that most

22 pediatric patients have preservation of lung function

1 and would be less likely in general to exhibit

2 hemoptysis.

3   When examining cases of hemoptysis by age

4 group, you can see that although less for pediatric

5 patients than adults, the rate of any hemoptysis in

6 pediatrics is four times that of control, and the rate

7 of serious adverse events in hemoptysis is twice that

8 of control.

9   The number when examined by age subgroup of

10 six to 11 years and 12 to 17 years continues to show

11 this disparity with a difference in hemoptysis events

12 even in the youngest group of patients. The sponsor

13 suggests that pediatric patients having lower baseline

14 FEV1 led to a higher rate of hemoptysis. Lower percent

15 predicted FEV1 at baseline in the younger age groups

16 may be an explanation for why younger subjects in

17 either treatment group experience hemoptysis more

18 frequently.

19   However, it is not a reasonable explanation

20 for why the difference between treatment groups in the

21 younger subjects should be larger than that of older

22 subjects.

1   The sponsor performed an additional data

2 capture which combined hemoptysis events reported as

3 adverse events and episodes associated with

4 exacerbation. There is still a higher incidence in the

5 pediatric/adolescent patients who received DPM 400

6 versus those who received control.

7   So, to summarize the safety data, after 10

8 percent of screened patients were removed prior to

9 randomization, specific events of acute bronchospasm

10 were not substantially different between groups.

11 Hemoptysis, although low in occurrence overall, was a

12 significant issue with twice as many serious adverse

13 events and severe adverse events in those treated with

14 DPM over control, regardless of age.

15   The issue of overall tolerability continued

16 to play a role, even if one could pass the MTT, with

17 additional adverse events due to cough, throat pain,

18 vomiting, and hemoptysis occurring more commonly.

19 These events were also a frequent cause for

20 discontinuation in the DPM group with withdrawals twice

21 as common in treatment versus control groups.

22   Specifically, for the pediatric population,

1 discontinuations due to adverse events were higher in

2 the treatment group over control, and hemoptysis

3 occurred in the DPM group three to four times as much

4 as in the control group. This was most notable in the

5 youngest pediatric group of six- to 11-year-olds with

6 all cases of hemoptysis occurring in the treatment

7 group versus zero in the control.

8   For the subgroup of patients with severe lung

9 disease, those on DPM had higher withdrawal rates as

10 well as higher rates of adverse events of hemoptysis

11 than those receiving control, mirroring that of the

12 general safety population.

13   Finally, I will discuss the framework for an

14 overall benefit/risk assessment of the DPM program

15 about which we would like you on the Committee to

16 discuss further this afternoon. Considering benefit,

17 we have seen from the analyses presented that Study 301

18 was positive but Study 302 was negative or equivocal.

19 Because of the missing data and differential dropout,

20 multiple sensitivity analyses were performed to support

21 the positive result for Study 301. And it was not due

22 solely to the way missing data were handled.

1   Another point is the range of effect

2 identified in these sensitivity analyses of roughly 50

3 to 83 mLs, or two and a half to four percent of the

4 absolute FEV1, a clinically meaningful effect? And a

5 separate but related issue is that the missing data

6 from Study 301 make it difficult to estimate the

7 overall treatment effect on

8 FEV1.

9   The dropout data create an apples-to-oranges

10 comparison of DPM chronic tolerators to control

11 patients who may or may not tolerate DPM, so that the

12 treatment effect may not be accurately defined. Also,

13 some secondary endpoints numerically favor DPM, but

14 none reach statistical significance. Therefore, there

15 is limited support to reassure us that the small change

16 in FEV1 is representative of other clinically

17 meaningful pulmonary improvement.

18   With regard to risks, DPM is poorly tolerated

19 in some patients as evidenced by those unable to

20 complete the initial mannitol tolerance test, and by

21 increased adverse events related to overall

22 tolerability. The number of withdrawals due to adverse

1 events for the DPM group was consistently twice that of

2 controls, and hemoptysis events were consistently

3 greater in DPM treated patients.

4   With regard to the pediatric population, the

5 data for efficacy is less convincing than for the

6 population as a whole, and increased rates of hemoptysis

7 are clinically meaningful events.

8   In closing, as you hear the charge to the

9 Committee, which will be delivered by Dr. Durmowicz

10 later this afternoon, and as you discuss the questions

11 posed to you, we ask you to keep in mind this slide.

12 The primary question for the Committee is whether the

13 submitted data represents substantial evidence of

14 efficacy and if the safety database is supportive.

15   This concludes the FDA's presentation. Thank

16 you for your attention.

17   DR. JACOBY: Thank you very much.

18   There is time for some well-focused and

19 concisely stated questions from the Committee, and I

20 would ask the Committee to limit your questions to

21 clarifying issues that we will need to make a decision

22 as to how you are going to vote on things. There will

 1 be further discussion of all of this before we have the

 2 vote.

 3   Yes, Dr. Blake. Clarifying Questions to the

 4 Presenters

 5   DR. BLAKE: I have a question about the

 6 primary endpoint. When the FDA had discussions with

 7 the sponsor, had the primary endpoint already been

 8 decided? And, if not, then how come some of those

 9 other secondary endpoints which you describe as being

10 more important if the drug is not a bronchodilator, why

11 weren't they selected as the primary endpoint?

12   DR. DURMOWICZ: Our discussion with the

13 sponsor around endpoints back in 2005/2006 time

14 delineated pretty much what would be required with

15 different endpoints. An FEV1 endpoint would require a

16 less long study if you will. An exacerbation endpoint

17 would require a longer study of at least a year to be

18 able to capture enough events to be confident in them.

19   We didn't select the endpoints for the

20 sponsor. We gave them the requirements for them, and

21 they selected them including the absolute change in

22 FEV1 as opposed to a percent predicted change.

 1   As you heard, and as we stated at the end of

 2 Phase II meeting in 2005, since FEV1 is not a

 3 bronchodilator and would be supposedly reflective of

 4 longer term, clinically meaningful changes in lung --

 5 in other endpoints, we stated that they needed to have

 6 robust support from secondary endpoints.

 7   Now, whether that meets statistical

 8 significance or not is an open question, because they

 9 are not necessarily powered for every endpoint that

10 they can have. But the fact of the fact that

11 especially for 301 they didn't pre-specify any

12 secondary endpoints, and everything is -- and nothing

13 is adjusted for Type 1 error, and the trend is not that

14 great, kind of shows a not favorable light on the --

15 beyond the FEV1.

16   So FEV1 alone would be the thing that really

17 is supporting benefit in that trial. I don't know if

18 that answered all your questions, but that is the

19 general framework which we were operating under.

20   DR. JACOBY: Dr. Greenberger?

21   DR. GREENBERGER: This has to do -- for Ms.

22 Zhou and Dr. Permutt on the sensitivity analysis. I

1 wanted to make sure I understood this. I am looking to

2 identify the very good responders such as the FEV1 gain

3 of over 100 mLs.

4   And if I read that right, I do not see a

5 difference between those treated actively and those

6 not. Am I correct to assume that it's pretty much the

7 same in terms of identifying the very good FEV1

8 responders? Or is that an overinterpretation?

9   DR. PERMUTT: I read it slightly differently,

10 sir. In Study 301 -- if it's easy, can you get my

11 Slide 8 back? So if you consider an improvement of 100

12 milliliters or more to be very good responders -- the

13 one before that, please. Thank you.

14   There is a difference. About 35 percent of

15 people in the active group had such a response, and

16 only about 28 percent of people in the control group

17 had such a response. So our best estimate there of

18 number needed to treat is about 14, but there does

19 appear to be some difference in the number of

20 responders to active drug as compared to the number on

21 control.

22   DR. GREENBERGER: And on the other study,

1 with 302, was it -- the lines were closer. Is that

2 correct?

3   DR. PERMUTT: They are about equally far

4 apart at that same point of 100. If you could show the

5 next slide, please. Yeah. So there is separation at

6 100, which I don't know if you can read the numbers,

7 but that's where the vertical line is. About the same,

8 a little more even, 45 or so to 35 or so.

9   DR. JACOBY: Yes, Dr. Wagener.

10   DR. WAGENER: This is related to the same

11 graphing technique. Did you look at either percent

12 change from baseline and categorize that way instead of

13 absolute numbers like 100, 150, 200? Or did you look

14 at percent predicted point change, either of those two

15 variables, in the similar type of graphing?

16   DR. PERMUTT: We did look at some of those

17 things. Feng, are we prepared to show any of them?

18   MS. ZHOU: In the briefing document, you can

19 find similar slides for the percent change and the

20 percent predicted change. In the briefing document

21 with similar graph separation.

22   DR. WAGENER: And from your perspective, does

1 it show essentially the similar pattern? Or was there

2 anything that the pattern looked distinctly different?

3   MS. ZHOU: It's similar in my point of view.

4   DR. JACOBY: Okay. We are going to break for

5 lunch. We will break for lunch for half an hour. Be

6 back at 12:36. You can leave your laptops here. If

7 you need any personal stuff, take that with you.

8   And I would remind the Committee no talking

9 about this among yourselves or with anyone else.

10   Thank you.

11   (A lunch recess was taken.)

12   DR. JACOBY: Okay. We're back.

13   Okay. We are going to have the open public

14 hearing speakers now.

15   The FDA and the public believe in a

16 transparent process for information-gathering and

17 decision-making. To ensure such transparency at the

18 open public hearing session, the FDA believes that it

19 is important to understand the context of an

20 individual's presentation.

21   For this reason, FDA encourages you, the open

22 public hearing speaker, at the beginning of your

1 written or oral statement, to advise the Committee of

2 any financial relationship you may have with the

3 sponsor, its product, and, if known, its direct

4 competitors. For example, this financial information

5 may include the sponsor's payment of your travel,

6 lodging, or other expenses in connection with your

7 attendance at this meeting.

8   Likewise, the FDA encourages you at the

9 beginning of your statement to advise the Committee if

10 you do not have any such financial relationships. If

11 you choose not to address the issue of financial

12 relationships at the beginning of your statement, it

13 will not preclude you from speaking.

14   The FDA and this Committee place great

15 importance in the open public hearing process. The

16 insights and comments provided can help the agency and

17 this Committee in their consideration of the issues

18 before them. That said, in many instances and for many

19 topics, there will be a variety of opinions. One of

20 our goals today is for this open public hearing to be

21 conducted in a fair and open way where every

22 participant is listened to carefully and treated with

1 dignity, courtesy, and respect.

2   Therefore, please speak only when recognized

3 by the chair.

4   Thank you for your cooperation.

5   There will be five minutes allotted to each

6 open public hearing speaker. We have nine speakers.

7 And at the end of four minutes and 30 seconds, the

8 light will change color there.

9   So may I invite the first speaker, please?

10 Open Public Hearing

11   MS. JENKINS: Are we on?

12   DR. JACOBY: Yes.

13   MS. JENKINS: Thank you. Thank you for this

14 opportunity to speak today. I am Carroll Jenkins,

15 executive director of Cystic Fibrosis Research,

16 Incorporated, or CFRI. We are a national 501(c)(3)

17 nonprofit dedicated to funding CF research and

18 supporting education awareness and advocacy for the

19 community.

20   I do have nothing to disclose, no financial

21 relationships to disclose.

22   I am also the stepmother of Alex, who is 38

1 with CF. Several years ago, I celebrated the marriage

2 of my stepson on the California coast. Alex, then in

3 his early thirties with CF, left the wedding with his

4 new bride for their honeymoon in a remote area farther

5 north, and I returned to work in Mountain View.

6   Two nights later my husband called to say

7 that Alex was in the hospital. He had hemoptysis. His

8 lungs were bleeding. A few years prior, Alex had had a

9 lobectomy on his left lung. Surgery removed that part

10 of the lung because it was so diseased. And now his

11 situation on the edge of life, he had been helicoptered

12 from the coast to a hospital in Northern California,

13 and then boarded a second helicopter to be admitted to

14 a hospital more familiar with cystic fibrosis.

15   Thanks to the emergency teams, Alex made it

16 to the hospital on time, and today he continues

17 teaching percussion and performing in the Sacramento

18 area. He touches lives with his gift of drumming. He

19 also devotes four hours every day to breathing

20 treatments and health care. Four hours.

21   I share this with you today not because the

22 story is extreme, but because stories of crises are

1 part of life for many people with cystic fibrosis. The

2 median age of survival continues to be extended, but

3 the quality of life for children, teens, and adults is

4 greatly compromised by cystic fibrosis. And while no

5 two patients are alike, the vast majority suffer from

6 respiratory illness. So what do these patients have in

7 common?

8   Ideally, mucus is an agent that helps --

9 helps to get rid of pathogens in the system. We all

10 breathe. We inhale. And we take in the fresh air or

11 dust from construction sites or droplets in the air

12 from someone's congested cough in an elevator or spores

13 in a moldy bathroom. We all breathe this air, and for

14 most of us the mucus in our airways and lungs captures

15 these pathogens in the ciliary beat and move that mucus

16 out. We cough and swallow and clear our system.

17   But for CF patients, the mucus is abnormal.

18 It is thick. Enter all that we breathe. And for those

19 with CF, much of it will stay, and the germs can grow

20 and colonize, causing a progressive decline in lung

21 function and premature mortality. Any drug that can

22 help a patient clear the mucus will bring a better

1 quality of life and a longer life to those with this

2 disease. Any way to even reduce the rate of decline in

3 pulmonary health, or stabilize health, is huge.

4   The cystic fibrosis community must have all

5 available treatments in their tool box. At CFRI, I

6 hear from people across the country about their

7 challenges and fears. CFers cough and cough, trying to

8 clear out their mucus, which they cannot do

9 effectively. They can even throw a rib in this

10 process.

11   If they could clear their lungs, they would

12 be stronger and healthier. The spiral of decline in

13 lung health might stop.

14   This community looks to medical science for

15 help. Right now, there are few available products for

16 muciliary clearance. I am hopeful that new medications

17 which address lung clearance and respiratory health for

18 CF patients will be available soon. We need more

19 options now.

20   I thank you all for your role today in this

21 process.

22   DR. JACOBY: Thank you, Ms. Jenkins. Our

1 next speaker, Emily Schaller.

2   MS. SCHALLER: Hello. I'm Emily Schaller.

3 I'm from Detroit, Michigan, founder/president of the

4 Rock CF Foundation, and I have no financial issues to

5 disclose.

6   So I'm 30 years old. I'm going to be 31

7 actually in about 22 days, and I have cystic fibrosis.

8 I was diagnosed in 1983, and at the time they kind of

9 told my parents, "Look, really beautiful baby, really

10 cute, but she probably won't live long enough to

11 graduate from high school." In 1983, the treatments

12 for CF, my parents had digestive enzymes, vitamins, and

13 then they used to beat me or do chest physical therapy

14 where I would spend 20 to 30 minutes at a time several

15 times a day to clear that mucus out, right?

16   Fast forward, we are 2013 now, and I have not

17 only seen the new drugs that have been developed and

18 that are on the market, but I have lived them, and

19 that's why I'm alive today. These treatments are

20 incredible. They are life-changing. They are giving

21 me life. They are giving my friends with CF lives.

22 And they are giving parents, you know, a chance to

1 watch their kids grow up and graduate from high school

2 and get married.

3   So because of these new drugs, I have been

4 able to speak around the world, kids with CF, families

5 with CF, and I hear a lot of things. And one thing I

6 hear is the treatment burden. These drugs are great

7 that I take, but I spend hours a day with these drugs -

8 - breathing treatments, chest therapies, 40 enzymes a

9 day. And these are just to keep me healthy each and

10 every single day, healthy but also healthy enough to

11 run half-marathons, cycle across states, and do half-

12 ironmans.

13   And this is my airway clearance, right? I

14 use these drugs in combination with exercise as airway

15 clearance. It is awesome.

16   And I couldn't be more excited. When I heard

17 about this drug and its potential and the device and

18 how it's delivered, super easy and it could save a lot

19 of time, which will allow patients with CF to do the

20 things they love, to run, to cycle, to go to college,

21 to get married, to be a father, and to live a life.

22   So this drug is going to hopefully change

1 lives, give patients more time to do these things that

2 they love, and reduce the burden of care for patients.

3   So thank you for letting me be here today,

4 and see you later.

5   DR. JACOBY: Thank you very much. Speaker

6 three?

7   DR. AITKEN: Good afternoon, everybody. I

8 think I have some slides of my own.

9   My name is Moira Aitken, and I was or am the

10 principal investigator of CF-302. But today I am here

11 under my -- for my patients' behalf and not on behalf

12 of Pharmaxis. So I have no conflict.

13   What I wish to do today was to stress the

14 burden of care that patients with cystic fibrosis have.

15 This is my own design input of just the pulmonary

16 medications that I ask my patients to fill out every

17 Monday morning. And on the yellow are nebulized

18 treatments that can be taken every day, and on the

19 white are nebulized antibiotics that are rotated every

20 month. And not clearly seen, but on the red arrows are

21 other very time- consuming medications, such as the

22 therapy vest and exercise, which we like in the Pacific

1 Northwest.

2   And so to emphasize this burden of care, I

3 thought I would give the example of three of my

4 patients, in addition to emphasizing that.

5   So pulmonary therapy, we are discussing. We

6 should really hear from the experts, so we have just

7 heard requires up to 180 minutes of pulmonary treatment

8 every day. And the nebulized therapies require time,

9 they require the equipment that has to keep working all

10 the time, and very importantly, as we just heard, an

11 electric supply. So that my patients, they go to

12 school, they go to college, they go to work, they try

13 to have a life. And it's difficult to transport that.

14   And so this device that mannitol is delivered

15 in is very easy to transport, and I can't emphasize the

16 importance of that.

17   And, finally, as a patient advocate, during

18 the open -- my patients were randomized, and I knew who

19 got what in the first six months. But during the open-

20 labeled phase of the study, all of the patients at my

21 site were clinically improved and taking mannitol.

22   And now I want to move on to actually my

1 patients give me -- gave me permission to try to bring

2 them into the room with me, so I would like to just

3 describe them a little bit.

4   This first lady is of very similar age to our

5 last speaker. She is 31 years old. Her lung function

6 is in the forties. She is infected with Pseudomonas

7 aeruginosa and with Staph aureus, and formerly,

8 interestingly, with mycobacterium avium complex that

9 was causing disease. And she has a large treatment

10 burden. She has hypertonic saline. She uses inhaled

11 aztreonam, alternating with inhaled cholistin. And her

12 burden of pulmonary care she estimates as being about

13 two hours and 30 minutes a day. And so this would cut

14 off half an hour and get her treatment time down to two

15 hours.

16   The next patient, this is a very hardworking

17 guy. He is 49 years old. He works full-time, he has

18 two kids, and he has an elderly father. And his lung

19 function now is hitting that 40 percent predicted, and

20 he wants to spend time doing bowling. As you can see

21 below, his club fingers, he is demonstrating his

22 bowling.

1   He is infected with Achromobacter

2 xylosoxidans and Staph aureus. Because he can't use

3 the inhaled antibiotics for Pseudomonas aeruginosa, his

4 burden of time is only one hour and 30 minutes. And

5 what he said to me to tell you -- and I'm sorry I

6 didn't quote the first person -- he said that "Mannitol

7 brings stuff right out of my lungs. It has a similar

8 effect to hypertonic saline, but is much more

9 convenient as I can take it wherever I want," including

10 going to his father's home to look after him.

11   "Hopefully, the FDA will do the right thing."

12 His words, not mine.

13   And the final person, this wonderful woman

14 playing her guitar with her mom there in the

15 background, she is a 32-year-old woman, FEV1 is about

16 40 percent. She has Pseudomonas aeruginosa and Staph

17 aureus. But interestingly, and very pertinent to the

18 discussion this morning, she has a real problem with

19 wheezing with inhaled antibiotics and other therapies.

20 And she is able to tolerate mannitol, and she said that

21 "Mannitol really got me cleared out."

22   So I am running out of time. But, in

1 conclusion, there is an urgent -- and I would argue

2 unmet, by these three examples -- need to improve lung

3 function, but at the same time reduce the burden of

4 care that we ask our CF patients to do.

5   Thank you so much for your time and

6 attention.

7   DR. JACOBY: Thank you, Dr. Aitken. The

8 fourth speaker?

9   DR. BOYLE: That's me. Hello. My name is

10 Dr. Mike Boyle. I'm an associate professor of medicine

11 at Johns Hopkins right up the street here in Baltimore

12 and run the Johns Hopkins adult cystic fibrosis

13 program, which cares for about 300 adults with cystic

14 fibrosis.

15   And the reason I am actually here today is to

16 ask you to consider approving this drug and to talk a

17 little bit about what -- as a clinician, I think where

18 it could potentially have the most impact in terms of

19 therapy.

20   You know, there has been a lot of good news

21 in terms of cystic fibrosis. We know there has been a

22 lot of improvements. More than 50 percent of our

1 patients now are adults. There is this longer life

2 span. A big part of that is because of being so

3 aggressive with new antibiotics. That has sort of been

4 the theme over and over again, new antibiotics, more

5 antibiotics, more inhaled antibiotics. That has been

6 very good.

7   I think one of the effects of that, though,

8 has been that there has been a little bit less

9 attention paid to the other key part of this cystic

10 fibrosis problem, and that is the airway clearance

11 part. And if you look at this, patients are having a

12 harder time having time to focus on the airway

13 clearance part, because of all of the time they are

14 spending with their inhaled antibiotics.

15   We also know that there really haven't been a

16 bunch of new developments in this whole area of airway

17 clearance. Really, the main one in the last 10 years

18 has been hypertonic saline. If you look at the data

19 for hypertonic saline, it definitely has efficacy. It

20 improves FEV1. It decreases exacerbations.

21   But there is one big problem: it is our

22 patients' least favorite drug. How do we know this?

1 Because we have actually looked at refill data from our

2 patients at Johns Hopkins. We followed 100 patients

3 for over a year, and actually looked in real life how

4 often they were filling their medications based on, you

5 know, each category.

6   Hypertonic saline was actually filled less

7 than 40 percent of the time it was prescribed. So

8 while in the clinical trial the hypertonic saline may

9 look somewhat impressive, in real life we know that

10 there are some limitations, because patients hate to

11 take it. Why is that? It takes a long time. It takes

12 20 minutes. And also, for many patients they have a

13 hard time tolerating it. They say it's way too salty.

14 It burns. They don't like it.

15   So what we really need is something to allow

16 us to be able to address this airway clearance area

17 that gives us another option besides hypertonic saline.

18   This is where I think that the dry powder

19 mannitol has such potential to impact our therapy in

20 this group. We know that -- from an efficacy

21 standpoint that there are very -- it was very

22 comparable in many ways to hypertonic saline, but I

 1 think the real-life efficacy is going to be even

 2 better, because this is something that is going to be

 3 faster, patients are going to be willing to take, and

 4 so it is going to actually be a significant improvement

 5 over hypertonic saline in many ways because of the

 6 real-life experience.

 7   The other part is the tolerability part. I

 8 mean, we know that there is going to be a subset of

 9 patients with any dry powder is going to have a hard

10 time tolerating that. Just like there is a subset of

11 patients with hypertonic saline who say, "I can't take

12 it."

13   But that is not the group that we are going

14 to prescribe this to. We are going to identify that

15 group that has a hard time with the tolerance test or

16 has a cough. We are not going to treat that group. We

17 are going to treat the group that is obviously showing

18 benefit, and that group is going to be able to have

19 more time, be able to go ahead and do their medication.

20   The last part I would say is this -- this is

21 a drug which I think is in many ways empowering. I

22 know that is sort of a strong word, but I take care of

1 adults. They are trying to do a lot of other things

2 with their lives. They need some extra weapons to be

3 able to address airway clearance, not have it take up a

4 big chunk of their day.

5   This is a type of drug where if we can have

6 some efficacy, find the right subgroup, this is going

7 to empower a group to be able to go ahead and do all of

8 the other things in life they want to do.

9   So I guess, in summary, what I would say is I

10 would really ask that you would consider approving this

11 drug for two things. Rather than focusing just on the

12 subset of patients who are going to have some side

13 effects from cough that we expect, just like all of our

14 other CF medications, we are going to identify that

15 group and we are not going to treat them.

16   Please think about the subset that is really

17 going to have the dramatic efficacy from this, get back

18 some of their life in terms of time, and allow us to

19 address that airway clearance area, which right now is

20 often lacking.

21   So thank you very much for your

22 consideration.

1   DR. JACOBY: Thank you very much, Dr. Boyle.

2   Speaker five, please?

3   DR. MARSHALL: Thank you for the opportunity

4   to address the Advisory Committee. I have no conflicts

5   of interest to divulge.

6   I was the adult CF program director at the

7   University of Utah for 14 years before joining the

8   Cystic Fibrosis Foundation. I asked to speak today to

9   the Advisory Committee to make sure that you fully

10 appreciate the treatment burden, and so in many ways I

11 am going to reiterate what others have said.

12   This is a young adult, you know, and behind

13 some of her treatments that she takes throughout the

14 day. And just imagine what -- how you would deal with

15 this treatment burden, or if this were your child how

16 he or she would deal with this treatment burden.

17   This slide is from a reference that was cited

18 earlier today, but actually shows the data from

19 Sawicki, et al., the study called Project on Adult CF

20 Care, PAC- CF, from Sawicki and colleagues. And it

21 quantifies the treatment burden for 204 adults across

22 10 care centers in the U.S. One hundred eight minutes

1 was the mean time spent on treatments, and you can see

2 the breakdown in the yellow bars, with 41 minutes

3 devoted to nebulized treatments.

4   This slide reminds us that efficacy, what we

5 have been talking about this morning, doesn't equal

6 effectiveness. And efficacy in clinical trials -- we

7 have talked about randomized clinical trials in the

8 real world where we are talking about clinical

9 effectiveness is impacted by adherence and subgroup

10 effects, the reality of day-to-day management, self-

11 management, and clinical care.

12   This slide from Eakin, et al. that was pushed

13 in The Journal of Cystic Fibrosis looks at adherence,

14 and it shows that adherence becomes problematic during

15 adolescence and emerging adulthood. This is data

16 derived from pharmacy refill data, and you can see in

17 those categories, particularly 19- to 25-year-old age

18 group, adherence really drops off.

19   Does adherence have an impact? Well, it's

20 clear, again from this same study, that poor adherence

21 is associated with more exacerbations. And as you have

22 heard today, exacerbations are important events in

1 cystic fibrosis. They are associated with morbidity,

2 mortality, decreased quality of life, and they are a

3 major driver of costs in health care.

4   This is data from our patient registry and

5 shows different birth cohorts with on the Y-axis

6 percent predicted FEV1, and age in years on the X-axis.

7 And what you can see here is even the youngest cohorts

8 -- look at that red line -- in adolescents their

9 pulmonary function starts to drop off. So this is a

10 critical time period in cystic fibrosis. It is also a

11 time period where exacerbations become more frequent.

12   So let's come back to the issue at hand

13 today, the mannitol. And I have put it here to

14 contrast with hypertonic saline in a class of drugs

15 that we call airway hydrators, or sometimes referred to

16 as airway hydrators. And of course I don't have time to

17 go through the details here, but in the review of this

18 Guidelines Committee that was referenced earlier this

19 morning, they came to the conclusion that hypertonic

20 saline and mannitol deserve the same recommendation, a

21 B recommendation, based on the certainty of the

22 evidence and net benefit.

1   You have heard about burden and convenience,

2 and they all weigh in favor of mannitol versus

3 hypertonic saline, which, as you have heard, must be

4 delivered by nebulizer. It takes up to 15 minutes or

5 so for treatment, as well as setup and breakdown time

6 to clean and disinfect the unit.

7   So when you factor this in, I think when you

8 start to look at things that are meaningful to

9 clinicians, adherence, and then clinical effectiveness,

10 you might speculate that mannitol might have an

11 advantage over hypertonic saline.

12   So, in summary, as the Advisory Committee

13 considers mannitol inhalation powder, I strongly

14 encourage you to keep two things in mind -- the

15 treatment burden that people with CF face each and

16 every day, and the importance of the distinction

17 between efficacy and clinical effectiveness in the real

18 world of clinical management and self-management for

19 people with CF.

20   Thank you.

21   DR. JACOBY: Thank you, Dr. Marshall.

22 Speaker number six, please?

1   MR. CAHILL: Good afternoon. My name is

2 Gerry Cahill, and I am no financial affiliation or

3 partnership with the drug company.

4   I am a volunteer at the Boomer Esiason

5 Foundation. I am 56 years old with cystic fibrosis,

6 currently on disability due to the progression of

7 cystic fibrosis. I gave up a great career that

8 hopefully I will go back to at some point very soon.

9   Over 30,000 people in the United States are

10 suffering from this awful disease. There is no cure.

11 The life expectancy is 38 years old. I have been one

12 of the fortunate ones that I am living and breathing at

13 age

14 56.

15   Due to the progression of my disease and

16 being very resistant to most medications, I had a

17 double-lung transplant nine months ago. I had trouble

18 breathing, could not keep my lungs clear of mucus, my

19 lung function was down to 19 percent. I was basically

20 drowning in my own mucus.

21   My only hope for survival was a double-lung

22 transplant. Lung transplantation is not a cure with

1 CF, and you trade one disease for the other, and there

2 is a lot of complications. People with cystic fibrosis

3 need more drug therapies and options in their life.

4   This is why I am advocating for this drug.

5 This drugs help clear your lungs. The new drug is

6 simple and quick to use for people with CF, and they

7 can spend more time living their life and enjoying

8 versus spending more time on doing therapies.

9   Life with CF is cut very short for us. So if

10 you can spend less time on therapies and more time

11 living life, then that is a blessing. It is all about

12 time management with cystic fibrosis.

13   Although all of us want a cure for CF, most

14 young adults and adults that you speak to who have CF

15 would tell you they want more therapies and options as

16 we await a cure. This drug is another treatment option

17 for people with CF. People with CF need more options.

18   Thank you.

19   DR. JACOBY: Thank you, Mr. Cahill. Speaker

20 number seven, please.

21   DR. ULUER: Good afternoon. And thank you

22 for this opportunity to speak before the Committee

1 today.

2   My name is Ahmet Uluer, and I am a

3 pulmonologist and director of the adult cystic fibrosis

4 program at Boston Children's and Brigham and Women's

5 Hospital where we care for over 600 patients. I also

6 participate on an advisory board, working on a quality

7 improvement program with Pharmaxis on educating on

8 airway clearance.

9   We have heard from our speakers today that

10 there is a relative, you know, paucity of treatments

11 available in CF, and, you know, every day, you know, we

12 look into our patients' eyes and we try to think of

13 what else we can -- you know, what else we have in our

14 armamentarium to use for our patients. And so, you

15 know, we -- and I feel that this medication adds to

16 that unmet need.

17   As Patrick Flume had talked about, and as

18 everybody else here had talked about, when -- you know,

19 we formulate a plan with our CF patient, but, you know,

20 after that clinic session is done, they enter the real

21 world and we don't know what our patients are going to

22 be -- you know, facing the real world and they make

1 decisions on what they are going to do.

2   Our adult patients, they are in school, they

3 are working, they have families, and, you know, who

4 among us have two or three hours a day to spend on

5 taking medications that will stabilize or -- you know,

6 stabilize the disease, let alone have to combat

7 exacerbation. And so most of the current interventions

8 are time-consuming, and respiratory equipment necessary

9 to deliver these therapies require proper use and

10 disinfection.

11   So despite our best hopes, when I have a

12 patient leave my clinic, they are faced with, you know,

13 a myriad of variables that make their decision,

14 depending on the weather, depending on if they are

15 going away on a trip, depending on, you know, just what

16 their day looks like, they are going to make decisions

17 on what treatments they are going to take.

18   And so if an option exists that might lead to

19 a more effective clinical outcome while decreasing

20 their treatment burden, we welcome that. We know that

21 poor adherence, as Bruce Marshall just showed, leads to

22 poor outcomes, and we know that when you are poorly

1 adherent - - I'm sorry, that when you -- poor outcomes

2 -- when you are poorly adherent, it will lead to poor

3 outcomes.

4   We also know that poor adherence comes from

5 complicated therapies. So it is difficult for us to

6 quantify, because we don't have any numbers that show

7 this, how the drug delivery system like bronchitol that

8 is simple and easy to use and store, you know, will

9 meet for improved adherence, but I think it's safe to

10 say will increase patient use of this class of therapy.

11   So based on our experience with other agents

12 like hypertonic saline, we think increased exposure to

13 this class of drug will help increase the chance for

14 improved outcomes. And we also know that this mode of

15 therapy has also demonstrated improved exercise

16 tolerance for our patients, so we believe promoting

17 exercise along, you know, with doing these therapies

18 can take -- can even provide a more profound benefit.

19   So I think it is reasonable to extrapolate

20 that an easy-to-use therapy that can accompany an

21 active child, adolescent, or adult throughout their day

22 will improve adherence among this population.

1   So appropriate attention is being given to

2 systemic therapies that directly impact a basic defect

3 in the pathogenesis of cystic fibrosis. And based on

4 our experience now with patients taking ivacaftor and

5 CFTR modulators, we have noticed that it is still very

6 clear to us that patients are going to need these modes

7 of therapies.

8   We have had patients experiment with stopping

9 their inhaled therapies, hypertonic saline or pulmozyme

10 and airway clearance while on ivacaftor, and we have

11 noticed that their lung function has dropped off. So

12 we know that this is going to be an important therapy

13 for even those patients, especially after they sustain

14 irreversible lung damage already.

15   So DPM, a therapy targeting the maintenance

16 of airway hydration, it is -- it has been shown to be

17 effective in improving lung function and hopefully in

18 increasing exacerbation-free days. So adding a safe

19 second option for appropriate patients targeting fluid

20 balance, and one that will improve adherence and

21 quality of life among patients, would be a welcome

22 addition and help increase our options for our families

1 and patients.

2   So as a clinician/researcher in the CF

3 community, it will be up to us to pursue comparative

4 effectiveness studies with similar drugs such as

5 hypertonic saline. But the current option to hydrate

6 has been effective for many, while others are having

7 difficulty tolerating this. So I do feel that it is

8 going to be important for our patient to have multiple

9 choices.

10   Our center focused on quality improvement

11 projects, looking at airway hydration, and we know that

12 that improved our lung function numbers and how

13 patients are doing in our center. So we know that

14 having another drug in this category is going to be

15 important to pursue in quality improvement projects in

16 the future, and so we look forward to having multiple

17 options for our patients to do so, as many of our

18 patients have not been able to either tolerate

19 hypertonic saline or have the time necessary to

20 administer it during their busy schedules.

21   Thank you.

22   DR. JACOBY: Thank you, Dr. Uluer. Speaker

1 number eight, please?

2   MR. SHARPE: Good afternoon, ladies and

3 gentlemen. My name is Ronnie Sharpe. I am the chief

4 community servant at Cystic Life. And Pharmaxis will

5 be providing an unrestricted grant to Cystic Life to

6 continue some of our programming.

7   First, I just want to thank you for letting

8 me be a part of this process. I'm a 32-year-old CF

9 patient. I have come here today to tell you about my

10 life and what you can do to improve it. I am a

11 University of Arizona alum. I'm a native of Arizona.

12 I'm a brother. I'm a Christ follower. I'm a son. I'm

13 a friend. I'm a sports fanatic. I'm an exercise

14 enthusiast. I'm a business owner. I'm a cystic

15 fibrosis patient. And, most importantly, I'm a husband

16 and a father.

17   I want to stress just how fortunate I feel to

18 be able to wear all of these titles. I have an

19 incredible life, and I am blessed to be exactly where I

20 am today, as the future didn't always look so bright

21 for me when I was born with cystic fibrosis in 1980.

22   Cystic fibrosis, the disease, and how it

1 affects the body hasn't changed over the years. It is

2 still the same genetic mutations affecting the way our

3 cells operate within our body. What has changed,

4 however, is the medications and the treatment options

5 available to us over the years.

6   I am here today thanks to people like you

7 helping to usher in new therapies to this community.

8 It is these medications and medical advances that allow

9 me to be here today, decades older than the expiration

10 date given to my mom when I was born.

11   It is these options that have allowed me to

12 say "I do" to my wife, and watch my daughter be born.

13   With that said, however, we still don't have

14 enough options, and current medications aren't enough.

15 We are certainly leaps and bounds ahead of where we

16 have been, but as a community we need more. What works

17 for some may not work for others, and that is why

18 options are so important. It is so important that we

19 can try a variety of medications to see what our body

20 responds to, so if we have the opportunity -- so we

21 have the opportunity to put ourselves in the best

22 position to succeed and take care of ourselves as best

1 we can.

2   As the options available to us have grown,

3 our life expectancy has increased, our health has

4 improved, and our quality of life has gotten better.

5 If you ask me, quality of life is one of the biggest

6 improvements that we can ask for. Added years are

7 important, but if you cannot live and live well, then I

8 feel there is little point to increasing life

9 expectancy, which brings me to something else that you

10 can bless me with today, and that is more time.

11   I know many, if not all of you, cannot

12 understand the treatment burden that CF puts on my

13 life. But all of you can understand time, because we

14 all value it and it is worth just as much to you as it

15 is to me. Like all of you, I have a lot of things I

16 want to do and need to do during the day. I need to

17 succeed at my job. I need to do work around the house.

18 I want to spend time doing silly things, like singing

19 the Hokey Pokey Dance with my daughter. I want to

20 relax in the evenings, to watch TV on the couch with my

21 wife.

22   But there is one aspect of my days that I

1 have to fit all of that around that many of you will

2 never have to accommodate, and that is my daily care

3 routine for my cystic fibrosis. My treatment routine

4 currently dictates my days, my schedule, my routine,

5 and, in many ways, my life.

6   I actually ran a stopwatch to give you an

7 idea of what I'm talking about. On Monday, I spent

8 three hours, 12 minutes, and 56 seconds doing cystic

9 fibrosis- related treatments and exercise. That is an

10 average day for me. To give you an idea, that is over

11 22 hours a week, over 96 hours a month, and over 1,150

12 hours per year. I spend 48 full days a year doing CF-

13 related treatments and exercise, and that doesn't

14 include my multiple hospitalizations each year.

15   Any treatment I can take that isn't a huge

16 burden on my time really excites me. Any potential

17 treatment option that I can take that can potentially

18 give me time back excites me even more.

19   So today I am asking you for two things. I

20 am asking you to provide me and my friends with more

21 options and more time. A positive recommendation for

22 bronchitol will do both.

1   Thank you.

2   DR. JACOBY: Thank you, Mr. Sharpe. And our

3 final speaker, speaker number nine?

4   MS. GRUMBINE: Thank you for giving me the

5 chance to share my experience with inhaled mannitol.

6 My name is Emily Grumbine, and I'm a 32-year-old

7 runner, a singer, a counselor, a tennis player, a wife,

8 and a volunteer living with cystic fibrosis.

9   I am able to do the things I love to do, and

10 I am able to function on a daily basis because I

11 currently take inhaled mannitol through the

12 Compassionate Use Program.

13   I was diagnosed with CF at three days old.

14 Over the years, cystic fibrosis has caused many health

15 complications for me, including CF-related diabetes,

16 elevated liver enzymes, and issues with my sinuses.

17 But my lung function, like most CF patients, continues

18 to be my biggest concern.

19   A significant amount of time each day must be

20 spent clearing out the thick mucus that clogs my lungs,

21 three hours a day of nebulizers, medicines, and chest

22 therapy, plus one hour of exercise. That can be very

1 overwhelming at times.

2   I religiously do everything in my power to

3 maintain my health. But despite my efforts, this

4 disease progresses.

5   In 2009, my CF specialist at Maine Medical

6 Center, Jonathan Zuckerman, told me about the

7 opportunity to participate in a clinical trial for

8 inhaled mannitol. He explained it was a dry powder

9 that, when inhaled, draws water to the airways, making

10 it easier to cough up the thick mucus in my lungs. I

11 thought to myself, this sounds awesome, and I jumped at

12 the opportunity.

13   When I reached the open-label part of the

14 trial, I was blown away with how much mucus I was able

15 to cough up after each of the 10 capsules inhaled. It

16 made me cough and the cough was immediately productive.

17 After a treatment, I could actually take a deep breath

18 without all the crackling, and my running started to

19 improve. I was able to run a little bit faster, a

20 little bit longer, as the weeks went on, and actually

21 enjoy it.

22   My energy was great throughout the day, and I

1 didn't feel such a burden breathing. Those 10 little

2 white capsules changed my life so drastically. Ten

3 capsules inhaled twice a day, three minutes twice a

4 day. That's the shortest treatment I have ever done.

5 Ten to 20 minutes is what I am used to with hypertonic

6 saline.

7   I actually felt like I was making progress

8 fighting this disease. I had such a positive life-

9 changing experience with inhaled mannitol that after

10 talking with my doctor we decided to pursue inhaled

11 mannitol through Compassionate Use. It took quite a

12 while but I was finally approved to receive inhaled

13 mannitol through Compassionate Use, and I took my first

14 dose on February 9, 2012. It was one of the happiest

15 days of my life.

16   I had been taking hypertonic saline, an

17 alternative treatment, to hydrate the airways, and my

18 health suffered during that time. My lung function

19 declined. I was much more congested all day, even

20 after treatments and exercising. My cough was less

21 productive and my energy just wasn't there. Even doing

22 the most basic physical activities felt like such a

1 burden on my breathing.

2   This past year has been stable health-wise.

3 I believe inhaled mannitol has a lot to do with that.

4 It has cut my treatment down by almost 30 minutes a

5 day. It has so much -- it is so much more effective

6 than hypertonic saline was for me. Because of inhaled

7 mannitol, with my 43 percent lung function, I was able

8 to run the Beach to Beacon 10K in August. Because of

9 inhaled mannitol, I am able to sing in church choir

10 every week without having a coughing attack. Because

11 of inhaled mannitol, I have more energy throughout the

12 day and I am able to function.

13   Because of inhaled mannitol, I have stable

14 lung function despite carrying the bacteria

15 Burkholderia cepacia. Cepacia is resistant to most

16 antibiotics, and often leads to an accelerated decline

17 in lung function for cystic fibrosis patients. I have

18 been able to maintain my lung function this past year.

19   I realize that this drug still treats the

20 symptom of a disease, as do all of the other

21 medications I take, but for most cystic fibrosis

22 patients we rely on drugs that treat symptoms and help

1 us maintain our health until the day we have a drug

2 that treats the underlying cause of CF.

3   To my knowledge, I have not experienced any

4 negative side effects from inhaled mannitol. It is

5 convenient, extremely effective, and time-efficient,

6 and I could not imagine my life without it at this

7 point. I want this drug FDA approved, so that I can

8 continue to use it, and so that thousands of other

9 cystic fibrosis patients here in the U.S. can as well.

10   Thank you.

11   DR. JACOBY: Thank you, Ms. Grumbine. And

12 thank you to all of the speakers. We appreciate your

13 presence here today.

14   That concludes the open public hearing

15 portion of this meeting, and we will no longer take

16 comments from the audience.

17   The Committee will now turn its attention to

18 address the task at hand, the careful consideration of

19 the data before the Committee as well as the public

20 comments.

21   Before we go on with the discussion portion,

22 the sponsor had answers to several questions that they

1 needed to gather data on, as well as at least one that

2 I think I cut them off on earlier. So, Dr. Fox?

3   DR. FOX: Thank you very much. If we start

4 with AA-2, please.

5   This is related to a slide I showed earlier

6 showing change from baseline at week six related to

7 week 26 and showing how they closely relate. What I

8 wasn't able to show you at the time -- if I can have

9 RS-23, please -- was the sensitivity and specificity of

10 that. And I think this may be very useful for you in

11 terms of understanding whether or not an opinion can be

12 made at week six in terms of tolerability or not.

13   If we go to the top line of this table, we

14 can see the proportion of patients who had any

15 improvement at all, which was about 60 percent, and we

16 can see in terms of the specificity and sensitivity of

17 how many of those people continued to respond at --

18 over the 26-week period.

19   So, conversely, we can be thinking about

20 patients who are not having any improvement and whether

21 there is a reasonable time point then to make an

22 opinion after an early exposure.

1   The next question I wanted to cover relates

2 to AA-4, please, which was about the mannitol tolerance

3 test. I have managed to find data from Study 302 which

4 looks at the cumulative dose of the MTT, which of

5 course goes up to 400 milligrams. And this is looking

6 at the mean drops in FEV1 based on those cumulative

7 doses, and it also provides the medians and ranges as

8 well. So hopefully this provides you the information

9 that you need to see that the mean change that -- at

10 the top end is about -- a drop in about 10 percent.

11   The last question that I wanted to cover,

12 unfortunately, I wasn't able to get a slide in time

13 which related to the -- how the screening values

14 related to baseline values in children and adolescents

15 in 302. I didn't get a chance to load the database

16 off, but what I can show you is that the -- that if you

17 plot those out they very closely relate to each other.

18 It didn't look like there was any signal outside that

19 would be explaining that, so there was no gross signal

20 of difference between sensitivity and specificity. So

21 it does look like that the regional change was a bigger

22 driver rather than age specific one.

251

1   And the last point I would just like to point

2   out as you go into questions is that we do have three

3   experts here that have spent all their working lives

4   dealing with cystic fibrosis, as I know a lot of you

5   have, too. So do please use their resource as well as

6   you go through your questions.

7   Thank you.

8   DR. JACOBY: Thank you very much, Dr. Fox.

9   We will now begin the panel discussion

10 portion of the meeting. Although this portion is open

11 to public observers, public attendees may not

12 participate except at the specific request of the

13 panel.

14   We will now have the charge to the Committee

15 presented by Dr. Anthony Durmowicz.

16   Charge to the Committee

17   DR. DURMOWICZ: Hello, again. I am going to

18 read the charge to the committee now, and I'm going to

19 also read through the discussion points and questions,

20 and then I'm going to hand the podium back to Dr.

21 Jacoby to moderate the discussion and then the voting.

22   It seems like you already probably understand

1 this, but I just wanted to put up the topic for

2 discussion -- slide, once again, to look at it at a

3 high level. From the efficacy standpoint, the big

4 question for us from a regulatory standpoint is, is

5 there substantial evidence of efficacy?

6   For this particular program, there is

7 confounding issues with the impact of missing data,

8 there is the multiple sensitivity analysis, and there

9 is the question of whether the effect is clinically

10 meaningful. We have heard a lot about safety, including

11 hemoptysis and tolerability issues. That is an

12 important safety discussion.

13   Safety and efficacy are both discussions in

14 the pediatric subpopulation. Is there sufficient data

15 to provide enough evidence that we are comfortable that

16 there is appropriate efficacy and acceptable safety in

17 the pediatric population?

18   I think it is important for the Committee and

19 people in the room to understand the regulatory

20 framework under which we operate in determining

21 efficacy. The Code of Federal Regulations, the CFR,

22 states that we must demonstrate, or it must be

 1 demonstrated, that there is substantial evidence

 2 consisting of adequate and well- controlled

 3 investigations.

 4   This is that the drug product will have the

 5 effect it purports, or is represented to have, under

 6 the conditions of use of -- under conditions of use

 7 prescribed, recommended, or suggested in the proposed

 8 labeling.

 9   Well, that is a little bit regulatory-ese, I

10 will admit, being a regulatory guy myself. But what

11 does that mean as we move forward? Typically, it has

12 meant that you need replicate, well-designed, well-

13 controlled studies demonstrating an efficacy finding.

14 This means two studies studying an appropriate

15 endpoint, both winning statistically and clinically.

16   The endpoint FEV1, as a surrogate endpoint

17 for improved lung function, fits into this category.

18 One positive study does not meet that bar. However,

19 there are times when one study may suffice. An

20 excellent design study showing highly reliable,

21 statistically strong evidence on an important clinical

22 benefit such as survival, may suffice.

 1   Also, a single study itself that demonstrates

 2 statistically and clinically meaningful benefit in

 3 multiple, unrelated endpoints can also suffice. As an

 4 example of this -- and the drug has been brought up

 5 several times today by both the -- both sides of the

 6 aisle, if you will -- the drug ivacaftor, which treats

 7 the entire disease cystic fibrosis and not just one

 8 aspect of it, that was -- the approval of that drug was

 9 based primarily on one adequate well-controlled trial

10 in adults and adolescents.

11   And that trial showed statistically strong

12 and clinically meaningful benefit in multiple

13 endpoints. That included FEV1, that included

14 exacerbations, that included weight gain. So that

15 would be an example of the type of study you would need

16 to fit into that category.

17   With regard to safety and the safety

18 standard, again, in the CFR, you would not approve a

19 drug if it did not include adequate tests to show

20 whether or not the drug is safe for use under the

21 conditions prescribed or that the results of the tests

22 that you did do showed that the drug is unsafe for use

1 under the conditions prescribed, recommended, or

2 suggested, or if the results do not show that the drug

3 product is safe under those conditions.

4   The fourth reason would be that there is

5 insufficient information about the drug to determine

6 whether the product is safe for use. Either of those

7 issues would not meet the safety standard.

8   Now, finally, let's just return to the

9 risk/benefit determination and take it in context. It

10 will be taken in the context that CF is a serious fatal

11 disease, and we have to think about, what are the

12 acceptable risks for a benefit? However, in trying to

13 decide to approve or not approve the drug, we still

14 need to meet that substantial evidence of efficacy bar

15 from a regulatory perspective. And that evidence is

16 the same for all drugs, including those for orphan

17 diseases.

18   Orphan diseases still need an evaluable

19 safety population as well. It might not be as big as

20 you would get in a COPD population, like we had in the

21 Advisory Committee yesterday, which numbers in the

22 thousands, but it still needs to be adequate.

1   That being said, I am going to read through

2   the questions and discussion points that the Committee

3   is going to be charged to discuss and vote on. And

4   following that, I will give the chair to Dr. Jacoby

5   once again.

6   The first question -- there are three

7   discussion questions and three voting questions. The

8   first question is basically to discuss the evidence to

9   support the efficacy of dry powdered mannitol at a dose

10 of 400 milligrams twice daily in improving pulmonary

11 function in patients six years and older with cystic

12 fibrosis.

13   The second discussion question is simply to

14 discuss the overall safety profile of dry powdered

15 mannitol. The third question would be to discuss the

16 support for efficacy and safety of DPM, dry powdered

17 mannitol, in children and adolescents. So it's a

18 specific pediatric discussion point.

19   Going to the voting questions, we will first

20 vote on efficacy. Considering the totality of the

21 data, is there substantial evidence of efficacy as

22 defined for dry powdered mannitol at a dose of 400

1   milligrams twice daily for improvement of pulmonary

2   function in patients six years and older with cystic

3   fibrosis? If not, what further efficacy do you

4   recommend?

5   Question 5 is the safety question. Is the

6   safety profile of dry powdered mannitol for the

7   maintenance/treatment of patients with cystic fibrosis

8   sufficient to support approval? Again, if not, what

9   further safety data should be obtained?

10   And, finally, we take both safety and

11 efficacy into consideration in what essentially is a

12 risk/benefit determination. And do the efficacy and

13 safety data provide substantial evidence to support the

14 approval of dry powdered mannitol at a dose of 400

15 milligrams twice daily for the management of cystic

16 fibrosis in patients age six years and older to improve

17 pulmonary function? That basically is the asked-for

18 indication by the applicant, Pharmaxis. And, if not,

19 what further data should be obtained?

20   So with that, I will hand the chair --

21   DR. JACOBY: Thank you, Dr. Durmowicz.

22   DR. DURMOWICZ: -- continued discussion.

1 Questions to the Committee and Committee Discussion

2   DR. JACOBY: Okay. Let's start with the

3 first discussion question, which is to discuss the

4 evidence to support the efficacy of dried powder

5 mannitol at a dose of 400 milligrams twice daily

6 improving pulmonary function in patients six years and

7 older with CF.

8   Okay. I take back everything I said about

9 being concise and not talking. Now is the time to

10 discuss this. Dr. Wagener?

11   DR. WAGENER: I'll throw my name tag on the

12 floor here. I'll start the discussion. I actually

13 would prefer this question if we separated the "above

14 18" and "below 18." But since that is not the way the

15 system works, having taken care of over 1,000 CF

16 patients in my career, I can certainly feel for the

17 comments that every patient and advocate has made.

18   At the same time, I think historically

19 therapies approved by the FDA are approved based on

20 statistical evidence of efficacy. And if we follow

21 that pure thought, in this case there isn't strong

22 statistical evidence by classic statistics that would

1 meet those guidelines and that was shown.

2   However, I would point out there may be a

3 couple of things a little different with this drug.

4 One is that it actually -- there is no FDA approved

5 drug that works in this fashion. There was the idea

6 this is to improve mucociliary clearance, and there is

7 no other FDA approved drug that does that. So this

8 would be really first drug in class.

9   And I guess my question is whether or not

10 that in some ways may change what you defined as

11 statistically proven efficacy.

12   The second thing is -- people have pointed

13 out very clearly is that this drug has some unique

14 properties in its evaluation in that it creates a side

15 effect that patients will tend to discontinue the drug

16 because of that side effect. We are assuming that this

17 10 percent plus dropout rate early on is because of

18 some side effect that the patient is experiencing.

19   Now, we may not have detected exactly what

20 that was, but they did and they stopped taking the

21 drug.

22   In the case of adults, I don't find that as a

 1 big problem, because if I give a medication to an adult

 2 that they find they don't want to take, they simply

 3 stop taking it. In children, that's not always true,

 4 and that's why I think the age separation may be very

 5 important.

 6   But in this situation perhaps that evaluation

 7 of just the patients who stayed in the trial does carry

 8 value, because those are patients who say, "I find

 9 benefit." And we may not be measuring the right

10 outcome. It may not be FEV1. It may not be

11 exacerbations. But it may be something else that -- or

12 it may not be qualify of life, because there was no

13 evidence there of efficacy. But it may be something

14 else that they perceive benefits them, and that's why

15 they stay on the drug and they continue it even through

16 the open label.

17   So having made that big prelude, what I would

18 say is I think there is evidence of efficacy. It may

19 not be based on some of the statistics that we have

20 used historically, but in a situation where you have a

21 life- threatening disease with no other drug in class,

22 I would be willing, as a member of this Committee, to

1 stretch the definition of efficacy beyond the

2 straightforward, simple, purest statistics, which I

3 greatly admire, but I think we have to go one step

4 further, and in this case I feel it should be shown --

5 or accepted as efficacious, at least in the adult.

6   DR. JACOBY: Thank you. Mr. Mullins?

7   MR. MULLINS: I would like to take this from

8 the standpoint of public health and the way the public

9 interprets our review of the evidence and their

10 perceptions of efficacy. And it is a very sensitive

11 issue when you begin to discuss a population that is so

12 passionate about hope, and so I am very careful to look

13 at their emotional state, to look at their desire for a

14 solution, on both sides of the issue, their desire for

15 some type of medical therapy that addresses their

16 serious concerns.

17   But the question is, what do they deserve?

18 Do they deserve something? Or do they deserve

19 something safe and efficacious? And that is what we're

20 talking about today. And I have some serious concerns,

21 as well as my peers here at the table, about efficacy

22 and safety.

1   The only challenge is, once a drug is -- a

2 therapy is approved, and it has a high level of

3 toxicity, and there are some indications of

4 intolerance, and there are some indications of serious

5 concerns and exacerbations and adverse effects, once

6 it's out there then it's out there. So those are my

7 concerns, and I certainly can relate to what Dr.

8 Wagener is saying.

9   But having dealt with public health issues

10 around the nation, the public believes that when we say

11 "safe," they believe safe. And so we're talking about

12 children, we're talking about people that somewhat feel

13 hopeless. And to play on their emotions, I am very

14 careful with that. So I think -- I know the decisions

15 that we make here should take into account sometimes a

16 group of patients that feel almost desperate.

17   So do you take that sense of desperation, and

18 do you take it to a higher level and produce and give

19 them something that is -- that meets all of their

20 desires, their wants, and is medically sound? And that

21 is the challenge of our decision, and I believe that

22 saying that we are almost there, or, yes, later, but no

1 right now, is something we consider.

2   But I will tell you that I like the direction

3 that we are heading. I like this desire for efficacy.

4 But to make a decision on desperation just to do

5 something, I tell you, we've done that in the past, and

6 you can look at the history of decisions that have been

7 made and sometimes that can come back to haunt you.

8   So I would tell you, just when you look at it

9 from a public health perspective, that the patients are

10 almost hopeless sometimes, but to take that sense of

11 desperation and play upon that, I would say to you that

12 just -- I would say to you that we have a significant

13 responsibility. And I would -- rather than lower the

14 bar, I would say raise the bar, because once it is out

15 there, they believe that it is totally safe. They feel

16 like that especially when parents are exposing this

17 particular therapy to the children.

18   Thank you.

19   DR. JACOBY: Dr. Greenberger?

20   DR. GREENBERGER: In the analysis, I'm going

21 to say that I think it might be time for the agency and

22 industry to take a look at the 1998 standards that we

1 just saw, and perhaps bring them up to date. And I'm

2 going to declare an academic bias, so to speak, because

3 I'm the senior author of a paper in The Journal of

4 Allergy and Clinical Immunology last year describing

5 what are called "endotypes of disease" regarding

6 asthma.

7   In other words, a specific subtype with

8 specific pathophysiology and presumably or possibly

9 specific treatment responses. In other words,

10 identifying the really good responders to the

11 medications and that would help identify the subtypes

12 of patients with certain diseases, such as in cystic

13 fibrosis, who do in fact get the better responses. And

14 that would allow a pathway forward for approving a

15 product that might not stand up to the 1998

16 requirements.

17   DR. JACOBY: Mr. Hawkins?

18   MR. HAWKINS: Thank you. I'm here as a CF

19 patient, not a scientist. So I'm going to focus my

20 responses on that aspect.

21   One thing about CF patients, and especially

22 those of us who are adults and have been living with

1 this all our lives, we have come to see that not all CF

2 therapies affect all of us the same way. And I believe

3 all of us know that there are going to be CF drugs

4 developed and approved by the FDA that aren't going to

5 help us the same way they do other people with CF.

6   So part of living with cystic fibrosis is

7 knowing that not every drug that is approved by the FDA

8 is going to be appropriate for each person with CF.

9 But also, we see that some of the drugs that may not be

10 appropriate for our friend help us a great deal. So to

11 find a drug that is appropriate or beneficial to every

12 person with CF, I don't think we have found that yet.

13 And we can't rule out all drugs just because we can't

14 say that they don't help anybody or they don't help

15 enough people. That's just the way I look at it.

16   Thank you.

17   DR. JACOBY: Dr. Parad?

18   DR. PARAD: I'm going to look to you for a

19 little guidance, this being my first panel experience,

20 regarding the slide Dr. Durmowicz showed talking about

21 efficacy standard and proposed labeling, which is not

22 one of our questions. But it was a statement that

1 ended "under the conditions of use prescribed,

2 recommended, or suggested in the proposed labeling."

3   So, you know, my take at the moment is along

4 the lines of Mr. Hawkins. I get the sense that there

5 is probably some efficacy for some patients. It may

6 not be a huge amount of efficacy, but there is probably

7 some for some people and there is room to learn about

8 how to figure out who those people are.

9   Safety is, of course, extremely important,

10 and I think we will talk about that in the next

11 question. But what I don't have a good sense for, if

12 what Mr. Mullins says is true, which I believe it

13 probably is, is that once it is out there, it is out

14 there.

15   How does this labeling control that? What do

16 we know from what has been done so far to put in the

17 labeling that might channel the use of the drug in a

18 way that would keep it to people who were studied and

19 not bump another drug out of the way that might

20 actually be more efficacious, even though it takes

21 longer to use.

22   And so are labeling considerations -- is

1 there anything that we can make in our decision that

2 would force the labeling to go a certain way?

3   DR. JACOBY: Dr. Durmowicz, could I ask you

4 to comment on that, please?

5   DR. DURMOWICZ: Sure. I will try to help you

6 out with that. When we talk about under the conditions

7 of use and labeled use with regard to the slide that I

8 showed, the first level that you are probably asking

9 about is the intended use is the indication, which is

10 CF patients six and older to improve pulmonary

11 function.

12   So even if you think that it is good for

13 adults and bad for children, that's the indication that

14 is proposed for use right now. So there is a caveat

15 there that you can say, "I think it's okay for children

16 and not for adults," or "I think it's okay for adults

17 and not for children."

18   With regard to the other conditions of use in

19 labeling, as I'm sure you're familiar because I know

20 you read every label of every drug you have ever had --

21 (Laughter.) -- that there are warnings and precautions,

22 there are contraindications, there are all of these

1 conditions of use as well. And they can be modified

2 and made more appropriate in which a drug would be more

3 acceptable to use in a certain population. We, on

4 purpose, did not want to go into labeling too much

5 today, other than to say that if you have a

6 recommendation which something should be put into the

7 labeling, that would be important for us to hear,

8 because then you are starting to talk about labeling

9 before you even talk about whether the drug is safe or

10 effective.

11   So in that context, I think that the first

12 bar is the indication, and then if you think it could

13 be used safety by having certain limitations of use or

14 certain contraindications, or something like that, then

15 I think that we would like to hear from you regarding

16 that.

17   I probably didn't answer you very well, but I

18 was trying.

19   DR. CHOWDHURY: I'm Dr. Chowdhury, and maybe

20 I can just add some thoughts here to your question, and

21 maybe also touch on a bit on the evidence of efficacy

22 that you are probably thinking about as you are

1 considering this discussion point or question.

2   The drug is proposed, as Dr. Durmowicz

3 mentioned, for patients with cystic fibrosis six and

4 older for improvement of lung function. And that is

5 what you are really considering as the conditions of

6 use. There is no specific limitations or restrictions

7 up there.

8   So if you have any thoughts after you vote,

9 you can let us know, and we can work with the company

10 around those conditions. So that's what -- as it goes,

11 and I'll pause because we have a question here.

12   DR. PARAD: But the indication of improving

13 lung function, is that restricted by the enrollment

14 criteria for these trials, to say that your FEV1 is

15 less than 90 percent or --

16   DR. CHOWDHURY: No, it is not.

17   DR. PARAD: No.

18   DR. CHOWDHURY: This really is for -- I'll

19 talk exactly paraphrasing what management of cystic

20 fibrosis in patients ages six and older for improvement

21 of lung function, not otherwise subspecified with any

22 criterias of pulmonary functions or anything. So that

1   is really what you are thinking about.

2   And as you are thinking about it, I just want

3   to go back and touch on a bit on the substantial

4   evidence, because this is really a very tricky point.

5   And part of what we're asking you is you've heard

6   everything from us, from the company, and from the

7   public, and have your own thoughts about it. So put

8   this all together and give your best thought and

9   recommendation to us.

10   And what we are laying out to you as we go

11 back and make a decision, what we are looking for, what

12 we are looking at, and we are sharing that with you

13 what Dr. Durmowicz laid out in the slide of substantial

14 evidence, per the Code of Federal Regulations, per our

15 guidance.

16   And the point here is we need to look at

17 substantial evidence, meaning two trials in most

18 situations, but we couldn't find it. The point was

19 raised first drug in the class. Well, this may be of

20 an indication life-threatening diseases. They are all

21 important, and we are all looking into consideration.

22 And we work with the company in helping develop such

1 drugs.

2   For example, foster development, priority

3 reviews, all we are given here. But going back and

4 evaluating for evidence of efficacy, we go back to a

5 substantial standard. So it really stands up to that.

6   In terms of life-threatening disease, it's

7 important to take into consideration, is it treating a

8 life-threatening aspect of the disease? If that is the

9 case, that becomes important. We are looking at a

10 surrogate, which FEV1 is, and you think about, is it

11 all that I care about, improvement of FEV1? Do I have

12 confidence that it will improve FEV1? And if it does,

13 then maybe other endpoints will improve. Generally,

14 two trials is what we are looking for in those

15 situations.

16   So this is what I wanted to share, so that it

17 can help you in your thinking process. And Dr.

18 Greenberger mentioned about subtypes, endotypes, that

19 they're important. And sometimes trials gets -- gives

20 a hint of efficacy, and then it will not be for all

21 patients and subgroups. And if somebody shows and

22 proves efficacy in their subgroup, then that becomes a

1 limitation of use, it works in that subgroup, and the

2 label can inform that. We don't have this for this

3 drug as in the previous label.

4   Thank you.

5   DR. JACOBY: Thank you. Dr. Blake?

6   DR. BLAKE: In looking at the regulatory

7 requirements, we have two trials that meet the primary

8 endpoints statistically and clinically. The first

9 trial does that; the second one doesn't. But it is

10 very close.

11   And I can't remember if any of the analyses

12 looked at whether there was an interaction by country

13 in terms of the outcome. And I bring it up only in

14 light of the Argentinian data showing, you know, in

15 those eight sites or whatever it was that there was a

16 decrease I think of -- in FEV1 and there wasn't even a

17 benefit.

18   So I just wondered if one of the countries

19 kind of drove the result of Trial 302 to make it just

20 barely not significant.

21   MS. ZHOU: There's no significant p-value for

22 the testing of the interaction for treatment by country.

 1 Selecting countries with extreme outcomes in terms of

 2 the treatment effect and excluding those centers may

 3 cause the overall results to go in the other direction.

 4 However, selcting centers based on a post-randomization

 5 outcome is not appropriate. We should not do that.

 6 I think that is not a fair way to treat the efficacy

 7 data.

 8   DR. JACOBY: Dr. Herring?

 9   DR. HERRING: So when I look at this, I see

10 two studies. Study 1 was the study with a very small P

11 value, but it was plagued by 30 percent or slightly

12 more in the treatment group missing data. There are no

13 patients from the U.S., and if you remember the plots

14 there was no difference in the children that is

15 statistically significant. And those lines the FDA

16 showed were just on top of each other.

17   And then, the study that followed at 302 was

18 a study that they had learned. There wasn't a lot of

19 missing data. They did not have a big problem with

20 missing data, but they did have U.S. patients, but it

21 wasn't statistically significant. And I would feel a

22 whole lot better if the order had been reversed, if the

1 small P value had come from the study without much

2 missing data.

3   And so to me the results are really mixed,

4 and I would love -- I would love to see the sponsor

5 find the population that this helps and to show that it

6 is effective in that population. But because of the

7 issues with the differential dropout, the control group

8 is not the same as those remaining on treatment.

9   And so, you know, this hasn't, in my mind,

10 been done yet. I would love to see that study. I

11 would love to have that population found and have

12 efficacy shown, and in that case I would be really

13 supportive.

14   DR. JACOBY: Mr. Mullins?

15   MR. MULLINS: I would just like to piggyback

16 on what Dr. Herring said. In going back to the issue

17 of public health and how the public will interpret our

18 analysis, they don't have the benefit of our

19 deliberations.

20   So what I -- I would feel much better about

21 saying yes if, rather than the presentation of the

22 therapy being a panacea, that it were strict -- there

1 were some parameters, there was a tighter profile on

2 efficacy. Then, I think the public could say, "You

3 know what? I understand the effectiveness of this drug

4 in relation to who I am," rather than it being

5 presented as, "Oh, this is for me," which leads to a

6 number of issues that we have seen in the past, because

7 the children will be forced to take it, because their

8 parents will say, "This is your medicine. You have

9 been prescribed this. You are going to stay on this

10 particular therapy," which concerns me with issues of

11 public health.

12   And so it's the presentation. If we would

13 have forthrightness from the sponsor, say, "Look, we've

14 studied this particular therapy. We see some -- we

15 understand why there is intolerance. We understand why

16 there is a high level of rejection or discontinuations,

17 and we have learned from this analysis." We would then

18 take that -- those best practices and interpret that

19 for the American public and give them the benefit of

20 knowing the profile of success for proper usage of this

21 therapy.

22   So those are my concerns, just piggybacking

1 on what you said, Dr. Herring.

2   Thank you.

3   DR. HARKINS: I agree it is underwhelming

4 data for efficacy, though my one thought is that these

5 patients are usually followed in a CF center with

6 physicians that have expertise in giving these

7 medications and would know what things to monitor. So

8 it wouldn't be like they are out there for -- I doubt

9 the general practitioner would prescribe this.

10   I think it would be someone that would have

11 more expertise in this patient population, that may,

12 you know, try this medication or at least be aware of

13 the side effects. But I agree; I am not overwhelmed by

14 the efficacy. It would have been nice if it had been a

15 positive thing in both studies.

16   MR. MULLINS: I just want 30 seconds. I just

17 wanted to say, Dr. Harkins, I can appreciate what

18 you're saying, but I have concerns about all of our

19 children don't have CF centers. We have children in

20 the public health system that are living in rural

21 environments, that don't have access to these -- the

22 benefits of a CF center. So they would be very

 1 vulnerable to our recommendations, and their parents

 2 would be interpreting this data or this recommendation

 3 on a very literal basis.

 4   So I would -- that's why our assessments and

 5 our recommendations have to take into consideration of

 6 the heterogeneity of our American public. So I do want

 7 to inject that.

 8   Thank you.

 9   DR. JACOBY: Dr. Tracy?

10   DR. TRACY: I'm going to have to kind of

11 respectfully disagree with my colleague here. I

12 actually practiced in a rural state, and that has been

13 my experience is that they may not go every day, but

14 they do get to the CF center pretty often.

15   The other thing I am struck with here is that

16 I am reminded that we take care of people, not

17 statistics. And I think we always have to keep that in

18 mind, and I'm further struck by the fact that CF

19 physicians that manage many of these clinics around the

20 country speak so strongly about that. That said, you

21 know, the data isn't, you know, particularly

22 overwhelming.

1   Thank you.

2   DR. JACOBY: Dr. Connett?

3   DR. CONNETT: I agree regarding the data

4 being fairly weak that the effect size is not large.

5   Dr. Dundore's presentation on C-16 I guess it

6 is stresses that one of the goals of CF treatment is to

7 lessen exacerbations. And what we have been talking

8 about mostly here is the surrogate FEV1 improvement,

9 and I think it could be a mistake to approve a drug on

10 weak evidence for a surrogate.

11   The standards of sensitivity testing and the

12 tipping point analysis and those sorts of things were

13 not applied for exacerbations or for hemoptysis. And

14 so I kind of feel like those analyses could have been

15 carried out as well, but it is not here.

16   DR. JACOBY: Dr. Castile?

17   DR. CASTILE: I feel like I have to comment,

18 and I guess I agree -- maybe this is the time to give

19 my take on this. After reviewing all of the material

20 and listening to all of the testimony, particularly

21 from the public, what I carried away is that there is a

22 borderline effect on FEV1 that is in the two to four

1 percent range. I think it was Ms. Zhou who stated that.

2 It rung a bell with me because that's what I carried

3 away when I came in the room.

4   Beyond that, there is no evidence at all of

5 any clinical effect. And so that is my summary of the

6 data.

7   I think, though, there are -- in the data

8 there is a suggestion that there is a -- and the

9 testimony, that there is a significant subset that may

10 benefit from the drug. And, again, what I gleaned from

11 looking at all of the data was that this subset

12 probably has an FEV1 between 40 and 70 and they are

13 probably adults. And that is both from the data I

14 looked at before I came and then some of the

15 presentation from the drug company.

16   And so it is quite a dilemma when you

17 certainly want to provide -- and I'm a provider -- that

18 kind of therapy to -- and what was striking about the

19 testimony was -- from the public is it was all from

20 people in adult -- well, adults with cystic fibrosis

21 and directors of adult centers, which kind of, in a

22 subjective way, verifies my sense that they have the

1 sense that it works in that adult population.

2   So I have quite a dilemma in terms of how to

3 think about this or how to vote, because I don't see

4 adult patients, but if I did I would kind of want that

5 option, you know?

6   The other comment I would have is that about

7 halfway through reviewing the massive number of pages

8 that I was sent, I was quite -- sometimes this is not

9 too interesting. I found this data just enthralling

10 and very interesting. But sort of halfway through it I

11 thought, this is the greatest preliminary data I have

12 ever seen.

13   And I began to think about how to design the

14 definitive trial. And then I stopped because I

15 realized this was the definitive data to answer these

16 questions. And so that's just my take on the whole

17 process so far.

18   DR. JACOBY: Dr. Parad?

19   DR. PARAD: I concur with Dr. Castile about

20 the efficacy issue. I was wondering whether we could

21 talk about defining the efficacy, because just looking

22 at the P value is not the whole story. And looking at

1 the effect size is not the whole story.

2   If we look at the history of what has

3 happened to CF treatment in the past 20 years, there

4 has been an incremental addition of things that make a

5 small improvement. And when those have all been added

6 together, the impact on meeting survival has been

7 pretty significant.

8   So, personally, I would say a two to four

9 percent increase in FEV1 doesn't sound like a very big

10 effect size, but that may be really -- adding it on to

11 all of the other things, may make a significant

12 difference to some patients. So if we are -- if we

13 have to agree on how we define "efficacy," I guess I

14 would propose maybe talking about whether that range of

15 FEV1 is an acceptable definition.

16   DR. JACOBY: Anyone have thoughts on that?

17 Mr. Hawkins?

18   MR. HAWKINS: I would say it is.

19   DR. JACOBY: Yes, I'm sorry. Dr. Wagener?

20   DR. WAGENER: I think you could take two

21 approaches. As with everything, one is you say

22 anything is better than nothing, in which case a one

1 milliliter improvement would be considered valuable.

2 And I would imagine if you asked just about any CF

3 patient that is what they would say, anything is

4 valuable.

5   Conversely, I would argue that adding

6 something if it has no burden, that may be true, but

7 everything we do -- we have been hearing how this has

8 less burden than some other therapies, such as

9 hypertonic saline. But it still has more burden than

10 nothing.

11   And if you gain one milliliter but the burden

12 is such that you end up not doing something else that

13 had greater benefit for whatever reason, then you have

14 lost. And that is where the risk is of accepting very

15 small steps, because you may lose even worse in

16 something else.

17   DR. JACOBY: Yes, Dr. Castile.

18   DR. CASTILE: Well, I think two to four

19 percent is pretty small, and it is in the range of the

20 variability of FEV1 in patients with cystic fibrosis.

21 But I sort of look at it in another light. What the

22 company did was tested this on a very broad population.

1   And the other thing, is this -- there is no

2 longer a virgin population. So that 50 and 70 percent

3 of the patients were already on things that clear mucus

4 in various ways, whether it's DNase or an oscillating

5 vest or whatever.

6   So in that light, it makes for me the two to

7 four percent increase -- I mean, actually, in thinking

8 about designing the next study, I can't reproduce the

9 previous studies on things like DNase, because the

10 population is not there. And so if the improvement

11 there -- and what I tell patients is it was somewhere

12 between seven and 10 percent in the various studies.

13   I don't think it's likely that if you take

14 that non-virgin population and add another hydrating

15 agent that you are going to get the same effect. So

16 that you get any effect that is borderline measurable

17 is actually fairly striking, and the biggest problem I

18 have is the breadth of the study and what subpopulation

19 it really helps the most.

20   DR. JACOBY: Yes, Dr. Druce.

21   DR. DRUCE: I'd just like to make just a few

22 comments about clinical study design in general as it

1 pertains to this and to the efficacy of this product.

2 And that especially in orphan indications, when it is

3 difficult to adequately recruit large populations,

4 there is a natural inclination to take -- or comes

5 especially when the endpoint is a surrogate endpoint

6 and it's not universally clear that a particular

7 endpoint is going to be valid.

8   It would of course be desirable to look at

9 outcomes and to look at a wider variety of secondary

10 outcomes on this particular product and ones like it,

11 but I think you have heard the difficulty of the cystic

12 fibrosis patients' life in conducting -- being able to

13 do this as well as getting involved in clinical trials

14 that are also burdensome.

15   So participating for 26 weeks in this type of

16 activity is a significant period of time, although, as

17 you have heard, you know, a longer trial might be

18 necessary to look at exacerbations.

19   So, again, if you were deciding or

20 considering further trials looking at endotypes,

21 looking at subpopulations, would really be much more

22 challenging in terms of recruiting patients in adequate

1 numbers to be able to conduct that type of a study.

2   Also, I would just bear in mind that looking

3 at endpoints in the area of mucociliary clearance is

4 particularly challenging. I mean, we don't even have

5 consensus about what is a cough, if we are looking at

6 cough studies. And so using something that we can

7 measure like FEV1 as a surrogate in this particular

8 case is obviously a surrogate, but it is something that

9 is measurable, and there is always a correlation that

10 the clinician has to take from the observed measurement

11 to what they think will be the benefit from the

12 patient.

13   And I think that you have clearly heard

14 certainly from the public and certainly from some of

15 the experts that there are people who do respond to

16 this particular medication.

17   DR. FOX: I would just like to point out that

18 we did do an extensive responder-type analysis to try

19 and identify a more optimal population, and we looked

20 at all of the key baseline features, based on gender,

21 FEV1, reversibility, an extensive list, all of the

22 different factors that we had that we could use.

1   None of these -- so this is the list that we

2 used to -- does that come up? I'm trying to get the

3 slide up there to show you the list, but it's not

4 coming up.

5   So you will see that this was an extensive

6 list of baseline risk factors that we did try and

7 evaluate, and what we found -- none of these were --

8 gave real clinical utility in terms of identifying a

9 specific responder population. And I think this

10 absolutely echoes the fact that patients need such

11 individualized therapy in CF there is this idea that

12 wouldn't it be great if we could know firsthand on the

13 specific phenotype of patient who would respond.

14   The fact is, in this case, the mechanism of

15 action of this drug does apply across a broad range.

16 The study was done in a broad range of patients, but

17 ultimately I don't think we could have designed a

18 study. First of all, it wouldn't be representative.

19 But, secondly, I don't think it would get us anywhere.

20 What we do know, though, is that patients who do

21 respond tend to stay responders, and those patients who

22 do not respond tend to stay non-responders.

 1   So, actually, I think far greater utility is

 2 based on the data that I showed you earlier, which

 3 relates to the fact that there is an opportunity for a

 4 very brief trial of therapy, reduced exposure in

 5 patients, but those patients who aren't showing

 6 anything, then those will be the patients that could be

 7 considered non-responders.

 8   Thank you.

 9   DR. JACOBY: Thank you. Yes, Mr. Hawkins.

10   MR. HAWKINS: I just wanted to remind

11 everyone that, you know, the only drug currently being

12 used for this role is hypertonic saline, which is not

13 FDA approved, and up until a couple of years ago had to

14 be compounded by outsourcing pharmacies.

15   So we are not replacing one approved drug

16 with another drug that we are trying to approve. We

17 are approving a drug for an unmet need or a not-

18 approved need.

19   DR. JACOBY: Okay. Mr. Mullins, yes.

20   MR. MULLINS: I guess the other thing I was

21 looking for from the sponsor also was just stronger

22 evidence, if you look -- look at time as a

1 consideration over the longitudinal analysis, it was

2 not encouraging to me, and I was looking for -- there

3 were some plateaus and there was -- you know, there was

4 some actual reduction in FEV1 over, you know, when I

5 look at weeks six to 26 and some of those analyses.

6   So that kind of concerned me also as far as

7 efficacy when you look at it from -- on a longitudinal

8 basis.

9   DR. FOX: On the longitudinal basis, I think

10 the data is quite remarkable, and the patients who did

11 show a response at week six were extremely likely to

12 remain responders. And I showed you the slide, perhaps

13 you remember, showing the relationship between response

14 at week six and week 26.

15   So showing the data in individual patients

16 rather than even just with the average data, we see

17 that patients who do respond at six weeks tend to stay

18 responders. So I think actually the longitudinal data

19 is very supportive of physicians being able to make a

20 decision early on.

21   MR. MULLINS: I guess I was looking at the

22 cumulative data when you look at post-marketing

1 analysis, when you look at -- when you look at post-

2 marketing analysis, that is what I was referring to.

3 And thank for that --

4   DR. FOX: So understood.

5   MR. MULLINS: Thank you for that   --

6   DR. FOX: That's a good --

7   MR. MULLINS: -- but I was looking on the

8 cumulative level. That's -- you know, when you look at

9 it, some of the analysis from South America, Argentina,

10 that is the kind of -- I was looking for more

11 trajectory, and I saw more -- some of the results I saw

12 didn't -- were not overwhelming, so --

13   DR. FOX: If I may respond, I mean, I think

14 that's a very valid point which is one of the great

15 beauties of the Cystic Fibrosis Foundation registry is

16 that we could actually track patients instead of just

17 six months or open label to a year that we have already

18 done. It would enable us to track patients for years

19 beyond. And the only way you can do that is actually

20 giving access to patients, to the medicine, to be able

21 to track them over a longer period of time.

22   DR. JACOBY: Thank you. Dr. Durmowicz?

 1   DR. DURMOWICZ: With regard to

 2   subpopulations, I think given the issues with the

 3   dropout and the data itself, that the most important

 4   subpopulation that you want to know about in trying to

 5   make a fair comparison are the population of tolerators

 6   taking the control medication.

 7   And to do that, you would have to give the

 8   patients the mannitol tolerance test, put everybody on

 9   inhaled mannitol for a certain predefined period of

10   time, define the tolerators, because the people

11   wouldn't tolerate it, and then randomize the drug and

12   control. That would give you the appropriate comparator

13   group in a clinical study.

14   That issue, the apples and oranges issue,

15   doesn't go away, even though, you know, one study was

16   positive and one wasn't.

17   DR. JACOBY: Thank you. Okay. So that's the

18   discussion of efficacy in patients six years and older.

19   Let's go on to the discussion of the overall safety

20   profile of dry powder mannitol.

21   Mr. Mullins?

22   MR. MULLINS: I guess very briefly, my

1 primary concern when I questioned the analysis of the

2 concern -- the signals from hemoptysis, and the

3 response from the sponsor was that's just -- when we

4 look at that particular -- we look at the high

5 occurrence of hemoptysis in children, and the response

6 from the sponsor was, "This is just an issue of

7 chance."

8   And that concerned me, and I think I need a

9 non- Vegas-style answer to -- you know, to understand

10 why there was this, you know, high occurrence, because

11 I think the American public needs to know, because we

12 need -- and then that would lead us to a greater

13 movement toward understanding -- better understanding

14 the profile of the optimal subpopulation that we are

15 talking about here.

16   So that is one of my primary concerns. I

17 think it's an issue, and I'd like the sponsor to speak

18 to that issue.

19   DR. FOX: Thank you. First of all, to

20 categorically make clear we are not saying this is

21 purely chance. We do recognize this as a signal,

22 particularly in children, and we take that signal very

1 seriously.

2   What we do not know at this point is the size

3 of that risk and whether that risk is manageable or

4 not. Our view is, as it stands, that the benefit

5 outweighs the risk, and that is manageable. But I

6 think it is probably more appropriate if you ask one of

7 my clinical experts than somebody who is the sponsor.

8   But I think what we think is so important is

9 that by doing a registry we could actually evaluate the

10 size of that risk. We can never evaluate that risk

11 effectively by repeating studies. It is not going to

12 get us anywhere. We really need to know, is this a

13 manageable risk? And the only way that can be

14 addressed is through registry data.

15   Remember, the vast majority of the U.S. CF

16 population is part of the Cystic Fibrosis Foundation

17 registry, so that would be a possibility. But I don't

18 know if I'm allowed to call on any of my experts in

19 terms of the manageability of risk. So I think I would

20 ask Dr. Ratjen, if I could, as he is the pediatrician

21 on the panel, in terms of his view on the manageability

22 of the risk that we see.

 1   DR. RATJEN: Yes. So it certainly is

 2 something that you should take seriously. There is no

 3 question about it. And hemoptysis in children overall

 4 is rare. I think we provided some data in the slides

 5 previously that the group of patients that had

 6 hemoptysis was somewhat more severe in their lung

 7 function than others.

 8   And you have to take into account it's a

 9 progressive disease, so a child that has a lung

10 function of, let's say, 50 percent is very different

11 from an adult who has a lung function of 50 percent

12 because of the progressiveness of the disease. So for

13 a child that would be severe disease.

14   These episodes of hemoptysis in children were

15 transient. They did not lead to long-term problems

16 with these patients, and overall these patients that

17 had hemoptysis did have some benefit in terms of lung

18 function. So I guess that's the question of the risk

19 versus the benefit.

20   I, as a clinician, would say that the risk is

21 acceptable for the potential benefit, but of course you

22 would also put this into account of making a decision

1 in

2 --

3   MR. MULLINS: But let me respond to that.

4 When you look at the data, the clarity of the adverse

5 events is very pronounced. The clarity of the

6 benefits, if we are looking at -- if we are doing a

7 risk/benefit analysis as far as public health is

8 concerned, the clarity and the conclusiveness of the

9 data as it speaks to efficacy is quite vague and

10 sometimes elusive.

11   But when we talk about -- as I mentioned,

12 when we talk about hemoptysis, and with several other

13 issues related to the toxicity of this treatment,

14 therapy is very pronounced. There is no, you know,

15 lack of clarity here.

16   So I think that is -- when you are doing the

17 risk/benefit analysis, if the benefits were so

18 pronounced and very clear to me, and to my peers, I

19 think that there would be an overwhelming gesture of

20 support for this therapy. But that's where I have this

21 consternation is trying to understand, okay, if we are

22 going to put the American public at risk with this high

1 level of toxicity, and this therapy, then what is the

2 win for them? That's where the window begins to close

3 for me.

4   So maybe you can help me with that.

5   DR. RATJEN: So I can understand that you

6 have to weigh one versus the other. I think one of the

7 issues is if you look at the efficacy data, one of the

8 ways you can look at it is to look at differences

9 versus control, and that is usually what you do in a

10 clinical trial.

11   But the -- what you see in these clinical

12 trials is that the control groups actually do see some

13 benefit beyond what we usually see in CF studies. So

14 we don't usually see that much of a change in the

15 control group in a clinical study, so I think that's

16 also important to take into account if you look at the

17 size of the treatment effect.

18   And I think the -- for me, as a pediatrician,

19 it is reassuring that these episodes of hemoptysis had

20 no long-term negative effect on those patients. And I

21 think it is important, as it was mentioned before, that

22 patients with cystic fibrosis, the overwhelming amount

1 of patients with cystic fibrosis are being cared for by

2 experts who have a lot of experience in that field, and

3 have a lot of experience with dealing with hemoptysis,

4 be it in children or in adults.

5   DR. JACOBY: Thank you.

6   DR. FOX: Could you perhaps comment -- slide

7 up, please. Professor Ratjen, I wondered if you could

8 comment on the clarity of the signal in terms of

9 hemoptysis risk when what we are really looking at when

10 we look at the exacerbation incidence in totality is

11 10.4 percent versus 7.6 percent.

12   So although we recognize as a signal, I think

13 it is important to remember these numbers.

14   DR. RATJEN: Well, it is also clear that the

15 majority of events we are associated with pulmonary

16 exacerbations -- where this is more commonly seen.

17 And, again, I don't want to downplay the risk of

18 hemoptysis. It certainly is an important consideration.

19 But, again, these were not long-term problems; these

20 were transient. And you have to consider that these

21 patients stayed on the medication despite the fact that

22 they had these opposite -- these episodes.

1   So, and that is usually not the case if there

2 is a perceived negative effect on the patient side as

3 well.

4   DR. JACOBY: Thank you. Dr. Witzmann?

5   DR. WITZMANN: Thank you. I would just like

6 to point out a few issues with regard to hemoptysis for

7 the Committee to consider. And the first is that these

8 issues of hemoptysis that I pointed out on my slides,

9 there were episodes of serious adverse event, and the

10 definition of serious adverse event includes things

11 such as hospitalizations or prolongation of

12 hospitalization.

13   And they were -- again, there was not a grand

14 number, but it was at a rate of eight or 2.2 percent of

15 the pediatric patients treated on the DPM group -- or

16 of the DPM group versus control of two patients. So

17 there is a difference in that group, and these patients

18 were all randomized.

19   And, again, getting back to the point, I just

20 wanted to also bring out the point with regard to these

21 patients in the pediatric group who had episodes of

22 hemoptysis in general did have much lower FEV1s than

1 one would think of for a general pediatric population.

2   However, the pediatric group was randomized.

3 Therefore, there is still an increased number of

4 patients in the DPM treatment arm who had more episodes

5 of hemoptysis than all of the pediatric patients in the

6 control group.

7   So the second thing I want to point out is

8 that this was not the analysis interpreting all of the

9 episodes of hemoptysis, whether they occurred with an

10 exacerbation or not. This was just the ones that were

11 reported by the investigators as adverse events. That

12 meant that there was something in that person's

13 clinical judgment that said that this was abnormal and

14 of concern, so I am going to report it.

15   Even when you take those number of patients

16 who may have been having an exacerbation and had an

17 additional hemoptysis, when the sponsor compiled that

18 data as well, which you have also seen, there was still

19 an increased number that was greater in the DPM

20 pediatric population than that of the control

21 population for the pediatric group as well.

22   So I just wanted out to point out those few

1   thoughts. Thank you.

2   DR. CHARLTON: Can I just clarify one point

3   about that? There were three SAEs of hemoptysis in the

4   six- to 17-year-olds. But the reason there were SAEs

5   is that they were hospitalized for the exacerbation

6   that was occurring at the same time.

7   DR. JACOBY: Thank you. Dr. Blake?

8   DR. BLAKE: In looking at this differential

9   risk in the pediatric patients, were there any -- this

10 is to the sponsor. Were there any data looking at the

11 lung dose, the amount of drug that actually reached the

12 lung of children versus the adults? To help maybe

13 clarify whether or not there was a difference in just

14 the amount of drug by their body size that might

15 explain some of it.

16   DR. FOX: I'm really sorry. Could you repeat

17 that question?

18   DR. BLAKE: Sure. In looking at this

19 differential risk of hemoptysis in children, did you

20 have any data that you looked at, say before the

21 clinical trials, to help determine what dose of drug

22 reached the lung in children? Maybe it was greater

1 proportionately than what was in adults that reached

2 the lung.

3   DR. FOX: So in terms of deposition by age, I

4 would like Dr. Dundore to cover -- cover in terms of

5 the distribution. What we do have in terms of dose

6 ranging based on FEV1 you saw already, but I think

7 you're asking a different question, which is how much

8 drug is actually getting into the lung, and, therefore,

9 should there be differential dosing based on

10 deposition.

11   DR. BLAKE: Right. I mean, if there is some

12 direct toxic effect of the drug onto the lung to cause

13 hemoptysis, then --

14   DR. FOX: Yes. So I'd like to --

15   DR. BLAKE: -- that's what I'm wondering.

16   DR. FOX: -- Dr. Dundore to talk about the

17 lung toxicity data, please.

18   DR. DUNDORE: We have not specifically looked

19 at the differential deposition in adults versus

20 children, but in adults the deposition of dose -- of

21 inhaled dose is about 25 percent.

22   DR. FOX: In terms of lung toxicity, have you

1 seen the panel study?

2   DR. DUNDORE: Oh, there is no -- in the

3 animal toxicity, there is no evidence of lung toxicity.

4   DR. RATJEN: It's a bit difficult to do this

5 for this drug in terms of looking at dosing in

6 different age groups, because you cannot measure levels

7 of this compound. It certainly has been done for other

8 drugs, including antibiotics that -- like tobramycin,

9 both for nebulizer solutions as well as for dry powder

10 preparations.

11   And there is no evidence to suggest that

12 there is an age dependency in dosing, so that younger

13 patients would get a higher dose, because deposition is

14 quite a complex issue and there are multiple factors

15 that play into it. But the bottom line is that for

16 those drugs that have been studied in cystic fibrosis,

17 there doesn't seem to be an age dependency in terms of

18 deposition, if you measure it by serum level, or for

19 DNase there is also some studies looking at

20 bronchoalveolar lavage where there wasn't an age

21 dependency of deposition.

22   DR. JACOBY: But none of those was done with

1 your device or your formulation or powder, you know,

2 particle size or --

3   DR. RATJEN: No. This is just the overall

4 pediatric experience. It is not directly related to

5 this device.

6   DR. JACOBY: Dr. Tracy?

7   DR. TRACY: Just a quick one. Might as well

8 go back up there. Have you thought at all about

9 mechanistic reasons for the hemoptysis in kids? You

10 said we really don't know much about toxicology. What

11 do you think is doing it?

12   DR. RATJEN: I mean, there is certainly -- I

13 mean, if you think about what the drug does in the

14 airways, so it clears mucus out of the lung, you could

15 expect if you clear mucus out of areas that have been

16 plugged up for quite a while that there is the

17 opportunity that there is some minor portion of

18 hemoptysis in the same setting.

19   So, and there is some irritation of the

20 airway causing cough, so it could well be this link

21 between cough and opening of mucus plugs.

22   But Dr. Bilton wants to say something,

1 because she has some experience with that.

2   DR. BILTON: Yeah. I mean, clearly, those of

3 us using the drug have thought a lot about the patients

4 who have had these small hemoptysis. One of the things

5 -- and people with CF, they come into my clinic and

6 they want to know -- "I have just coughed up a bit of

7 blood. Is it the toby that I'm taking? Was it the asli

8 (ph) that I started?" And clearly there is a signal

9 here in children that we need to take seriously.

10   My experience with some of the patients --

11 and I am an adult physician -- but it relates to this

12 suddenly getting up a lot of horrible dark sputum, and

13 patients describe coughing up thick coral-like cast

14 structures. And I wonder if when they are coughing

15 those up they are exposing a grazed, bleeding airway.

16   The events Dr. Charlton can speak to, but

17 they were more predominantly towards the beginning of

18 the trial, not towards the end. And the majority were

19 not recurrent.

20   Now, clearly, we need to follow this up.

21 Clearly, a registry study would help, but I wonder if

22 some of the hemoptysis is part of the effect of the

1 drug of clearing stuff that has been stuck down there.

2 But I can't say that is, but it's one of my hypotheses.

3   DR. TRACY: So your thought is it may not

4 necessarily be the drug per se, but the effect of the

5 drug.

6   DR. MILTON: Yeah. It may be part of the

7 efficacy, a side effect of the efficacy. But I can't

8 say that definitively, and I do believe that's why we

9 need to follow these patients up in the CF centers.

10   And the fact that patients stay on the drug

11 is a signal to me that they are weighing up the

12 balance. I fully appreciate with children you have to

13 be very careful. The adults can choose for themselves.

14 But that is one of my theories.

15   DR. JACOBY: Dr. Wagener?

16   DR. WAGENER: So I find the issue of safety

17 to be the biggest concern here. The efficacy, at least

18 for adults, I can feel pretty comfortable with, but the

19 safety is a big thing and I want to just mention two

20 areas. One is what we have been talking about and that

21 is hemoptysis.

22   Hemoptysis is a relatively uncommon thing in

1 pediatrics, and to see the numbers bump as much as

2 these did I think cannot be underestimated as far as it

3 could be something. It would be interesting to know if

4 they have looked at inflammation or some of these other

5 issues that might be related. So that is one thing I

6 think, particularly in pediatrics, throws a lot of

7 caution.

8   The second, though, is a longer term question

9 of safety. Since these studies were just six months

10 long, and even the extension study, I don't know how

11 much data they have collected beyond lung function on

12 that, there didn't seem to be a lot reported, at least

13 looking through the files that we had originally.

14   A chronic irritant may have chronic injury --

15 create chronic injury to the airway, and, as such,

16 particularly in children -- remember, children are not

17 just small adults. Particularly in children with a

18 growing airway, I would worry that this is a drug, if

19 approved, is not going to be limited to just the severe

20 lung disease patients.

21   It is going to become used in all degrees of

22 lung disease, and, in fact, people, if anything, will

1 interpret it the opposite of what we are, and they will

2 be saying, "Gee, since you are 120 percent predicted

3 lung function, we'd better get you on this medicine to

4 prevent it falling."

5   If there is a long-term adverse effect

6 creating inflammation, or something of this type, then

7 we are going to be creating a real problem that we may

8 not recognize for a couple of years. And, yes, the

9 Foundation registry with help us with that, but it

10 seems like we need to maybe know some of that data

11 earlier.

12   DR. JACOBY: Dr. Greenberger?

13   DR. GREENBERGER: My question is on safety

14 from the -- I believe it was eight sites in Argentina.

15 Were there excessive or a disproportionate number of

16 safety findings there, in that the efficacy data did

17 not coincide with the other centers around the world?

18   DR. FOX: I don't have that specific safety

19 data by country available now. Obviously, we do have

20 it available. It's not something we prepared. What

21 might be useful, though, would be to ask Dr. Ratjen to

22 comment on his experience -- he has visited a number of

1 South American sites -- in terms of the care available

2 in the United States compared to the care in South

3 America, and perhaps why we may have seen this rather

4 anomalous result.

5   DR. RATJEN: I think what the data from

6 Argentina shows is not necessarily a lack of change in

7 the group treated with 400 milligrams of DPM, but also

8 a huge control effect. And we know that the overall

9 level of care in Argentina is different from North

10 America.

11   We know that the outcome of patients in

12 Argentina, unfortunately, is much less favorable than

13 it is in North America as well.

14   To pin this down to certain factors is

15 difficult, but to me my interpretation of the data in

16 Argentina is that there was a trial effect that exceed

17 the trial effect in any other country. The patients

18 that were entered into the trial did get overall better

19 care, and, therefore, you saw this effect in both

20 groups in terms of improvement of their status.

21   In terms of adverse events and serious

22 adverse events, I don't think there was a clear signal

1 from Australia, but I have to give this back to Dr.

2 Charlton in order to comment on it.

3   DR. CHARLTON: I meant Argentina.

4   DR. RATJEN: Yeah.

5   DR. GREENBERGER: Argentina is what I'm

6 talking about.

7   DR. RATJEN: Oh. So I didn't want -- I

8 wanted to say Argentina. Sorry. And I have to

9 apologize to my Australian colleagues who are not here.

10   DR. GREENBERGER: So you think perhaps the

11 care was superior to the other CF centers in Argentina,

12 and maybe that explained the difference.

13   DR. FOX: So we did look for a center effect

14 as well, and we seem to be -- there is a consistent

15 control effect across the Argentinian centers that we

16 didn't see elsewhere.

17   So Dr. Ratjen's slide up, please. So this is

18 the data by center, so it is variable in terms of the

19 degree of control effect, but it is quite remarkably

20 different to -- these are very small numbers of course

21 in each center, but it is quite remarkably different to

22 the patent that we saw throughout the rest of the

1 world.

2   Just a brief point to an earlier point about

3 whether hemoptysis risk increases over time. We did

4 look at the incidence of hemoptysis in the first six

5 months, and we compared that to -- yes, slide up,

6 please. And we compared that to the incidence, then,

7 in the open-label phase.

8   So the patients on bronchitol, who then

9 continued the incidence, although slightly lower

10 numbers by the way -- this is a percentage -- 9.4

11 percent incidence and a 6.8 percent incidence in the

12 open label. So it doesn't look like there is an

13 increase.

14   On the other hand, the control group, who

15 then switched to receive 400 milligrams, did see a

16 small increase. So it suggests that this isn't

17 something that increases over time, but it does give

18 some veracity that this is -- this could be a real

19 signal rather than just a numerical difference.

20   DR. WAGENER: Although let me point out on

21 that that only 250 of your 360 patients continued, and

22 the 100 that dropped out may have been all the ones

1 with hemoptysis. And so what you are left with are the

2 patients who never had hemoptysis and now they're

3 having it, so --

4   DR. FOX: Well, except, of course, that

5 patients with hemoptysis in children actually

6 continued. So had it been patients withdrawing because

7 of hemoptysis, that would absolutely be the case. And,

8 in fact, we see the reverse, that the patients with

9 hemoptysis were continuing. So I think that's -- so I

10 think the data is probably quite useful.

11   DR. JACOBY: Mr. Mullins?

12   MR. MULLINS: I would just like to caution

13 against -- there has been a lot of discussion on

14 burden. I would caution against shifting the burden of

15 safety to the consumer, and the reason I say that is

16 because there is a lot of discussion about if you live

17 near a CF center, and have the benefit of excellent

18 care of my colleague Dr. Tracy, where everyone doesn't

19 have all of these parameters, these unique situations

20 where they can handle that burden of safety.

21   So I would just caution against saying,

22 "Well, if they have this and they have this and they

1 have a CF center and they have excellent care, then

2 they will be okay." Because there are a lot of people

3 -- and if you study our numbers in American public

4 health, we are struggling. Some of our pockets in our

5 cities struggle with public health and public health

6 issues.

7   So I would say that our ability to give them

8 something that is in a condition where it does not

9 shift that burden on them, because many consumers are

10 trying to manage their personal care. That's why

11 they're having problems. So that's what I did want to

12 inject.

13   DR. FOX: I think that's an important point,

14 and certainly we would be willing to discuss with the

15 FDA about whether there should be any issues about

16 which -- what type of sites should be able to provide

17 this medication. That would be one method to ensure

18 only experts would be using this drug in their

19 management. That would be one possible way I guess.

20   DR. JACOBY: Dr. Parad?

21   DR. PARAD: I was just thinking about the

22 conundrum with the control and wondering whether -- I

1 know from your earlier phase trials that you used 40

2 milligrams. And this is an unusual study in that your

3 control is a low dose of the drug, which could

4 potentially have an effect. Do you think it's possible

5 that six weeks of using 50 milligrams could have some

6 cumulative effect that might be causing the control

7 level to be higher than we would expect?

8   DR. FOX: We are left with -- I don't know.

9 The 40 milligrams used in the Phase II is virtually

10 identical to the 50 based on the 40 -- based on the

11 number of capsules and the emitted dose. So using a

12 number of five milligram capsules would equate almost

13 exactly to the 50 milligram we use for the 10 capsules.

14   So the dose is the same. The time is less

15 for sure. And I guess if that was the case, then the

16 effect estimate in children is conservative. But it

17 really is speculation; the Phase II data doesn't

18 support that.

19   DR. JACOBY: Dr. Druce?

20   DR. DRUCE: This morning I believe we saw a

21 slide with the incidence of hemoptysis in the CF

22 population in general. I think it would be quite

1 informative if there were any data available on the

2 incidence of hemoptysis and adverse events in general

3 from hypertonic saline, which is another airway

4 irritant.

5   And I would ask either the sponsor or the

6 experts if there are any data available to inform that

7 decision.

8   DR. FOX: If I could ask Dr. Flume to

9 comment as an expert in hemoptysis epidemiology.

10   DR. FLUME: And if I could have that slide

11 up, please. This is the slide that I had shown earlier

12 looking at what is known about the incidence of

13 hemoptysis, keeping in mind that how it was catalogued

14 in the past has varied. So, for example, in our CF

15 patient registry, in the past it had only been

16 capturing massive hemoptysis. So it was not capturing

17 all episodes of hemoptysis in patients.

18   So the Israeli paper was the first one to

19 actually look back into their charts to try and

20 determine what the incidence of the hemoptysis was.

21 And even in their paper, they admit that whatever they

22 could report is likely an underestimate, because they

1 are relying upon retrospective reports.

2   And so what you saw in that, of their patient

3 population which had a mean age of the low twenties,

4 had a nine percent incidence in that year of

5 hemoptysis. And I stated earlier 25 percent of those

6 cases are under the age of 13, so, obviously, there is

7 another chunk in there in the adolescent age group.

8   We know from the studies of rhDNase,

9 tobramycin, and even ivacaftor what the incidence of

10 hemoptysis was, because that was tracked as part of the

11 measurement they were using in the Fuchs criteria,

12 which did capture that question. And you see that in

13 the rhDNase study 21 percent incidence, and the mean

14 age of the study was roughly 18 years of age. Now,

15 again, that was in the '90s, and so we didn't have

16 quite so many therapies.

17   And perhaps as lung health has improved over

18 time, maybe that incidence will have decreased. But

19 you see the same thing in the tobramycin study. These

20 are patients who are required to have Pseudomonas in

21 their cultures. And then, most recently, the ivacaftor

22 study - - this is in the last couple of years -- you

1 can see a 22 percent incidence, and that includes

2 adolescents and adults.

3   So one of the things that we say is

4 anecdotally we see hemoptysis actually pretty

5 frequently, and I think some of our patients who have

6 had episodes of hemoptysis tend to ignore what they

7 perceive as being minor, that they have had it before.

8   Now, in our CF guidelines, what we had asked

9 of our experts is, what do you think about the first

10 episode of hemoptysis, even if it's scant? And the

11 consensus was that that warrants a phone call. That

12 warrants instructing the family to contact their

13 clinician. It doesn't mean they have to be in the

14 hospital, doesn't mean you have to jump all over it

15 with that, but the other part is most people consider

16 that to be a sign of an exacerbation, and that usually

17 warrants an intervention.

18   So this is what we know about the actual

19 incidence of hemoptysis, which I believe is, although

20 less common in children, is not negligible.

21   DR. JACOBY: Yes, Dr. Witzmann.

22   DR. WITZMANN: I would like --

 1   DR. RATJEN: I just wanted to make a brief

 2 comment related to hypertonic saline, because that was

 3 part of the question. And, unfortunately, because the

 4 large trial on Australia that was done on hypertonic

 5 saline, unfortunately, it wasn't done in a very

 6 vigorous way that all of the side effects were

 7 captured. So we don't have any good for that, so,

 8 unfortunately, we do -- we cannot compare that.

 9   DR. JACOBY: Yes?

10   DR. WITZMANN: Thanks. I'd like to comment

11 just a little bit upon those as well. As Dr. Flume did

12 point out with those studies, the studies that he

13 posted where we are discussing the incidence of

14 hemoptysis that was seen in those, while some of the

15 patient age ranges could overlap with the study that

16 we're looking here, this study was done in patients

17 where 43 percent of the total safety population was in

18 patients less than 18 years of age.

19   Just as an example, the patient populations

20 with regard to pulmozyme, while being done in the

21 1990s, also looked at a patient population, and one of

22 the two studies for registration for that trial looked

1 at patients who had a low FEV1 and were in the severe

2 category. So some of that data is skewed by the fact

3 that the patient population FEV1 range may have been

4 different as opposed to potentially the age ranges in

5 the study. So we think that's an important fact.

6   The other thing is Dr. Flume used this

7 information from the previous studies earlier to say

8 that looking at the study for pulmozyme, looking at the

9 study from toby that led to enrollment, that it's not

10 really fair to compare the groups when you are talking

11 about the overall FEV1 improvement, because so much has

12 changed. FEV1s, in general, have risen, as we saw from

13 Dr. Marschall's slides from the CF Foundation over

14 time.

15   So then to turn that around and say that,

16 well, maybe it does count if they are looking at

17 incidence of hemoptysis, and using the same data

18 doesn't necessarily - - isn't exactly equitable as far

19 as my interpretation of the same data.

20   Thank you.

21   DR. JACOBY: Dr. Greenberger?

22   DR. GREENBERGER: Severe acute hemoptysis or

1 any form of hemoptysis, can someone tell me how many

2 patients had to have bronchoscopy because of

3 hemoptysis? And in what groups?

4   DR. CHARLTON: There were 16 cases of

5 hemoptysis in the six- to 17-year-olds. Every single

6 case was medical management only. All but two of them

7 it was observation only. Two had medical treatment.

8   DR. GREENBERGER: Do you have the information

9 how many were hospitalized because of hemoptysis?

10   DR. CHARLTON: None were hospitalized because

11 of hemoptysis. Three were hospitalized because the

12 hemoptysis, in almost all cases, was associated with

13 exacerbation. Three patients were hospitalized for

14 intravenous antibiotics to treat the exacerbation.

15   DR. GREENBERGER: So no one was hospitalized

16 because of the --

17   DR. CHARLTON: Sorry?

18   DR. GREENBERGER: -- hemoptysis in the

19 absence of an exacerbation?

20   DR. CHARLTON: How many?

21   DR. GREENBERGER: You're saying no one was

22 hospitalized --

 1   DR. CHARLTON: Yeah. Sorry. No one was

 2 hospitalized --

 3   DR. GREENBERGER: -- independent of

 4 exacerbation.

 5   DR. CHARLTON: -- apart from being

 6 hospitalized for an exacerbation. The other thing to

 7 remember is that this -- the population in the study,

 8 because we had a cutoff of 90 percent FEV1, so this

 9 group of children and adolescents represents probably

10 less than half of what you would normally see in a

11 clinic. So the percentages overall are skewed.

12   DR. JACOBY: Dr. Durmowicz?

13   DR. DURMOWICZ: I just want to respond to

14 that comment, because you unequivocally can't say that

15 nobody was hospitalized due to hemoptysis when

16 hemoptysis is part of the definition of an

17 exacerbation. So I don't buy that comment. I'm sorry.

18   DR. JACOBY: Okay. Let's discuss Question 3,

19 which is a discussion of the efficacy and safety

20 profile in children now limited to the -- children and

21 adolescents limited to the age of six to 17 years.

22 Yes, Dr. Wagener

1   DR. WAGENER: I'll start this one off, too.

2 I was thinking of this as risk/benefit. But when I was

3 in grade school, I was told I can't divide by zero. So

4 if you look at the subgroup analyses, you cannot find

5 benefit in the under 18-year-olds. It is that simple.

6 And so if there is any risk, then it is infinity.

7   DR. JACOBY: Well, it's hard to argue with

8 the mathematics of that. Dr. Fox?

9   DR. FOX: Right. Well, obviously, I have

10 already shown you the forest plot -- the data slide up

11 -- that actually shows no statistical difference

12 between children and adolescents compared to adults.

13 So I think in terms of saying there is no effect, the

14 studies were designed to look at the overall efficacy,

15 and we certainly can concur with the FDA that although

16 there may have been some slight overestimate in terms

17 of Study 301, the effect and estimate in both studies

18 is around the region of around 60 mLs, and that is

19 equally applicable to the children and adolescents as

20 it is to the adult population.

21   The studies were designed to evaluate the

22 overall population, and there is no statistical

 1 difference between the two. Nevertheless, if I might

 2 have the next slide up, please, what may be useful is

 3 to look at the pooled data in six- to 17-year-olds that

 4 hasn't been shared to this point, looking at the key

 5 endpoints in children and adolescents, using the pooled

 6 data to decide whether there really is any evidence or

 7 not.

 8   And I would like to ask Dr. Ratjen to

 9 comment, to give a clinical overview from a

10 pediatrician on the clinical meaningfulness, if that is

11 all right, Dr. Jacoby.

12   DR. RATJEN: Okay. So this kind of

13 summarizes the data for FEV1 in mLs and FEV1 in percent

14 FVC, and also in terms of exacerbations. And I think

15 the way that I would look at the data, of course, if

16 you look at the individual data you don't see an

17 overwhelming statistically significant effect except

18 for FVC.

19   But the totality of the data all go in the

20 same direction, that there seems to be a benefit. And,

21 again, in the slide that I showed earlier today and

22 when you look at children versus -- in treated versus

1 control, there was certainly a significant control

2 effect. And overall it didn't really -- yes, slide up,

3 please.

4   If you look at these data in terms of change

5 in mLs, and taking into account that mLs in children

6 are actually a little bit more than they are in adults,

7 these data to me would not suggest that there is a --

8 that there is a bias that children have less efficacy

9 of the drug. In terms of the safety considerations,

10 absolutely that is something that you need to balance

11 against that and that's -- but I think I would

12 challenge the concept of saying that there is clearly a

13 different signal for children in terms of the lung

14 function response.

15   DR. JACOBY: Dr. Terry?

16   DR. TERRY: The question we are being asked

17 to discuss is support for the efficacy and safety. And

18 you are using FEV1 as a surrogate for efficacy, and

19 would argue that in fact it is a very poor surrogate.

20 We have no evidence that in fact the quality or

21 quantity of these people's lives are improved on the

22 basis of their FEV1.

1   DR. RATJEN: If we could go back to the slide

2 I showed on six- to 17-year-olds summarizing the

3 different endpoints of efficacy including exacerbation,

4 certainly recognizing your point about the surrogacy.

5   Slide up, please.

6   DR. FLUME: So when we debate which are the

7 proper endpoints, we look at all of the factors that

8 might flow into how our patients feel and function.

9 The FEV1 is the one that we use most commonly in the

10 clinic. It's the one we follow in the clinic. It's the

11 number our patients recall, they look at, they see. We

12 monitor it very closely, and that's one of the things

13 that we report in our data.

14   So you can carve that several different ways

15 by looking at it as a percent of predicted, keeping in

16 mind that this is a population which also is intended

17 to grow. So you don't want it to remain flat; you want

18 that to increase.

19   If you look at the other endpoints here, the

20 secondary input is looking at mechanisms of action in

21 terms of airway clearance. Earlier studies looking at

22 mucociliary clearance had demonstrated benefit in here.

1 If it's a fair surrogate looking at sputum weight, you

2 are seeing clear evidence of that there is increasing

3 weight.

4   And then I want to comment about

5 exacerbations, because I have heard comments being said

6 about that we didn't get it on the exacerbations.

7 Keeping in mind the study wasn't powered to measure

8 exacerbations -- that would require a very long and

9 large study to do that -- and yet what you see is a

10 clear signal of a direction in where we're going with

11 exacerbations.

12   And you saw this in the overall data. You

13 see a reduction there as well in the pediatric

14 population. And if I could have my -- the exacerbation

15 slide from the core?

16   I had shared with you the exacerbation rates

17 that came from other pivotal trial studies, one of

18 which you might recall is rhDNase, and that was

19 essentially its indication. Slide up, please?

20   And what you see here is a 28 percent

21 reduction in exacerbations. Actually, the decreased

22 incidence of exacerbations used in their primary

1 analysis was 22 percent and had a P value of .11. It

2 only got to 28 percent when it was done and age-

3 adjusted calculation was added in terms of the

4 analysis.

5   The reduction in tobramycin, that was not

6 part of their primaries either. It was a secondary,

7 and they only got that by doing a pooled analysis,

8 which we did not do in the analysis of the DPM. And

9 the hypertonic saline was entirely a post-hoc analysis

10 in terms of how that was done.

11   So these are all data that are out there in

12 which the Pulmonary Guidelines Committee has reviewed

13 these data and come to the conclusion that they find

14 sufficient evidence that they do in fact reduce

15 exacerbations. And I put this up to show the

16 exacerbation rate -- the reduction in exacerbations

17 that was seen in the dry powder mannitol and put them

18 into relative comparison of what you see with other

19 common drugs that we use.

20   DR. JACOBY: Dr. Durmowicz?

21   DR. DURMOWICZ: In response, I don't think --

22 we don't think you can make anything out of the

1 exacerbation data as far as any improvement in

2 exacerbations.

3   We talked to the company. We have told them

4 for exacerbations you'd need to look at one-year safety

5 information in a study. Secondly, you don't pool

6 exacerbation. We have never pooled exacerbation to

7 determine any benefit. And, thirdly, the exacerbation

8 data suffers from the same issues as the primary

9 analysis does with the differential dropout. And that

10 could be even worse in an exacerbation-type population,

11 because these patients are dropping out and they might

12 -- are the ones that might actually have more

13 exacerbations.

14   So I don't believe that there is any benefit

15 shown in exacerbations in this clinical program,

16 although you can show some nominal changes.

17   DR. JACOBY: Dr. Zhou?

18   MS. ZHOU: I want to clear about the power

19 calculation. Based on the SAP report on the Study

20 301/302, the sample size was estimated based on the

21 demonstrating an improvement in FEV1 of mannitol or the

22 patient, and a change in exacerbation rate across all

1 of the patients.

2   And from the -- in the original design for

3 the study, calculation based on 240 patients is enough

4 to detect the FEV1 difference. Because exacerbations,

5 they increase 100 subject, so power for the

6 exacerbation, 80 percent.

7   DR. FOX: The primary analysis was based on

8 FEV1, and we did indeed also power the study to show a

9 50 percent reduction in exacerbations. And certainly I

10 acknowledge that in my presentation. The issue is that

11 reductions far less than 50 percent are still

12 considered clinically meaningful. Slide up, please.

13   And the size of a study needed to show a 20

14 percent reduction in exacerbations with an 80 percent

15 power would need to be two and a half thousand. I

16 could certainly ask one of my clinical experts what

17 their view is on a 20 percent reduction in

18 exacerbations and whether it is clinically relevant.

19   Obviously, our studies were underpowered to

20 look at exacerbations that were still clinically

21 relevant. If I could ask Dr. Flume to comment on that.

22   DR. FLUME: So I know quite a bit about

1 pulmonary exacerbations, having studied it and written

2 about it for the last few years. When we talked about

3 exacerbations -- and much of what you have been seeing

4 are only those exacerbations which are related to IV

5 treatments, in this U.S. population in the last year,

6 that is 20,000 events -- 20,000 admissions for IV

7 antibiotics.

8   And when you start calculating the number of

9 estimated exacerbations that include oral antibiotics,

10 45,000. So when you start talking about reductions in

11 that, you are talking about a 20 percent reduction, is

12 that clinically relevant? It indeed is. In terms of

13 our patients, that is a big difference.

14   DR. JACOBY: Okay. We are going to take an

15 eight-minute break. Be back at 3:01.

16   (A recess was taken.)

17   DR. JACOBY: Before we get to the voting

18 questions, Dr. Flume is going to make a brief statement

19 about the CF registry.

20   DR. FLUME: For those on the Committee who

21 may not be familiar with the CF Foundation's patient

22 registry, this is a patient registry which is managed

1 by the Cystic Fibrosis Foundation. There are about 120

2 centers that contribute information on their patients.

3 This encompasses over 90 percent of the CF patients

4 that are in the United States, so we are capturing all

5 of them.

6   And most centers are consistent with my

7 center; 99 percent of our patients have signed consent

8 for participation. We are including data at every

9 encounter, including lots of clinical information.

10   So I know there have been concerns about

11 public health issues, but I just wanted to make sure

12 everyone knew what actually goes into the patient

13 registry.

14   DR. JACOBY: Thank you.

15   Okay. For the voting questions, we will be

16 using an electronic voting system for this -- for the

17 meeting. Once we begin the vote, the buttons on your -

18 - these buttons on your microphones will start flashing

19 and they will continue to flash even after you have

20 entered your vote until all of the votes have been

21 entered.

22   Please press the button firmly that

1 corresponds to your vote. If you are unsure of your

2 vote or you wish to change your vote, you can press the

3 corresponding button until the vote is closed. After

4 everyone has completed their vote, the vote will be

5 locked in. The vote will then be displayed on the

6 screen, so there is no secret ballot here. It is going

7 to have your name up and how you voted. Everyone will

8 know. That's part of the record here.

9   The DFO will then read the vote from the

10 screen into the record. Next, we will go around the

11 room and each individual who voted will state his name

12 and their vote into the record. And you can also state

13 the reason why you voted as you did. We will continue

14 in that manner until all the questions have been

15 answered and discussed.

16   So the first voting question is Question 4.

17 Considering the totality of the data, is there

18 substantial evidence of efficacy for DPM at a dose of

19 400 milligrams twice daily for improvement of pulmonary

20 function in patients six years and older with cystic

21 fibrosis? If not, what further efficacy data should be

22 obtained?

 1   We have discussed this question, but any

 2 final brief statements about this, Dr. Parad?

 3   DR. PARAD: These questions are not

 4 modifiable, I assume?

 5   DR. JACOBY: No.

 6   DR. PARAD: Okay.

 7   DR. JACOBY: Okay. So we are ready to vote,

 8 then.

 9   (Pause.)

10 Okay. Everyone has voted.

11   DR. HONG: We have three yeses, 11 nos, and

12 zero abstains.

13   DR. JACOBY: Okay. Let's start over here to

14 my left. Dr. Herring? Everyone, state your name, how

15 you voted, and then briefly why you voted that way.

16   DR. HERRING: Sure. Amy Herring, voted no.

17 The results presented by Pharmaxis certainly suggest

18 future studies are worthwhile, and the testimony

19 provided by the CF patients and their doctors suggests

20 that there may be real benefit in a subset of

21 individuals.

22   However, the sponsor has not yet met the

1 standard of evidence for efficacy of DPM overall or in

2 the population of DPM tolerators. The sponsor has not

3 shown that DPM is effective among children and

4 adolescents.

5   DR. JACOBY: Dr. Tracy?

6   DR. TRACY: Jim Tracy, and I voted no. I

7 looked at this principally from a regulatory

8 standpoint, and I agree with the previous comments

9 about lack of evidence.

10   I do, however, believe that there is no doubt

11 in my mind that there is a subset of individuals that

12 would benefit greatly from this drug. We just don't

13 know who they are yet.

14   DR. JACOBY: Mr. Mullins?

15   MR. MULLINS: My rationale for voting against

16 efficacy for dry powder mannitol was based on a couple

17 of things. Primarily, based upon DPM's performance

18 against control; and, secondly, for the post-marketing

19 analysis and the cumulative data, if you look at it

20 from a meta- analysis standpoint.

21   Thank you.

22   DR. JACOBY: Dr. Greenberger?

1   DR. GREENBERGER: Paul Greenberger. I voted

2   no. This is a huge unmet need. However, based on the

3   regulatory standards that are in use now, the data did

4   not support substantial evidence.

5   DR. JACOBY: Dr. Terry?

6   DR. TERRY: Peter Terry. I voted no for the

7   same reasons enumerated by Dr. Herring.

8   DR. JACOBY: David Jacoby. I voted no. I

9   don't feel that the evidence reached the standards set

10 by the FDA for approval.

11   DR. BLAKE: Kathryn Blake. I voted no. I

12 didn't feel like it met the standards set forth by the

13 FDA, although if we had been given the opportunity to

14 vote just on adults, then I would have supported an

15 efficacy for adults. But I just didn't feel like the

16 data was strong enough in children.

17   DR. JACOBY: Dr. Stone?

18   DR. STONE: Kelly Stone. I voted no. The

19 data presented didn't meet the efficacy standard,

20 particularly for children.

21   DR. JACOBY: Dr. Connett?

22   DR. CONNETT: This is John Connett. I voted

1 no. I agree regarding the efficacy standards. I think

2 it was interesting that the first trial had poor

3 followup rates and a lot of missing data and had a

4 positive signal. The second trial, they improved a lot

5 on the missingness, but the efficacy went away. So I

6 think there might be a message in that, too.

7   Also, we were asked to approve this for age

8 six and higher, and I can't go along with that complete

9 range.

10   DR. JACOBY: Dr. Harkins?

11   DR. HARKINS: I voted yes, partly because of

12 the unmet need. I did think one trial, even though it

13 had missing data, did have a signal. The second trial

14 also had a signal, and I think that it might have

15 utility in the CF population.

16   DR. JACOBY: Dr. Wagener?

17   DR. WAGENER: Jeff Wagener. I voted yes. I

18 felt that using the modified intent to treat approach

19 they took in 301 supported efficacy. The review by the

20 FDA in some ways supported efficacy for adults but not

21 for children. And I feel, overall, as Dr. Hawkins --

22 Harkins said. There is a modification to the absolute

1 definition of "efficacy" in a situation where this is

2 first drug in class.

3   DR. JACOBY: Dr. Parad?

4   DR. PARAD: I voted yes. I wanted to answer

5 a different question, but I'll give my provisos here.

6 I believe that 301 overall did show an effect, and 302

7 was marginal. I don't see this for children, but I do

8 believe that I would accept a two to four percent

9 response in this setting as an efficacious response.

10   But I would only consider it under -- if I am

11 allowed to give the suggested labeling that was

12 mentioned before, only under the supervision of a CF

13 center in greater than or equal to 18 years of age with

14 an FEV1 40 to 90 percent, a negative mannitol challenge

15 response demonstrated six weeks after therapy by

16 increased FEV1, and only under the circumstances that

17 there would be continued trials under informed consent

18 to look at the risks in subpopulations.

19   DR. JACOBY: Dr. Castile?

20   DR. CASTILE: Bob Castile, and I voted no,

21 because I thought that the FEV1 surrogate data was

22 borderline over the population from six to adulthood.

1 And there was no supporting additional evidence of

2 direct clinical benefit. And so I voted no, and I

3 think that there -- that further efficacy data should

4 be obtained.

5   DR. JACOBY: Dr. Cataletto?

6   DR. CATALETTO: Mary Cataletto. I voted no.

7 I was -- I have to say I was very impressed by the

8 clinical anecdotes, both from the public and from the

9 CF centers, but I did not think that the data merited

10 the standard of care or met the standard of care.

11   DR. JACOBY: Thank you. Okay. The second

12 question, Question 5. Is the safety profile for DPM

13 for the maintenance and treatment of patients with

14 cystic fibrosis sufficient to support approval? If

15 not, what further safety data should be obtained?

16   And we have discussed this quite a lot. Any

17 final thoughts on this before we vote?

18   (No response.)

19 Okay. Then, vote.

20   (Pause.)

21 Okay.

22   DR. HONG: We have three yeses, 11 nos, and

1 zero abstains.

2   DR. JACOBY: Okay. Same procedure. Let's

3 start at the other end this time, and we can come

4 around this way. Dr. Cataletto?

5   DR. CATALETTO: I'm Mary Cataletto. I voted

6 no. Same thing; I don't think it met the standard --

7   DR. JACOBY: Turn your microphone on.

8   DR. CATALETTO: Sorry. Mary Cataletto. I

9 voted no. I don't believe it met the standard for

10 approval.

11   DR. CASTILE: Bob Castile. I voted no. I

12 think -- I thought the data -- I think there was

13 agreement that there was an increased risk of

14 hemoptysis, particularly in children, that was not

15 explained yet, even taking into account the explanation

16 that bleeding may be a positive sign, a positive effect

17 of the drug.

18   In fact, I -- anecdotally, I would agree with

19 that. But I don't think we know the answer, and so,

20 again, I think we need more information.

21   DR. JACOBY: Dr. Parad?

22   DR. PARAD: This is Richard Parad. I voted

1 no, again, because of the wording of the question. I

2 would have said yes for 18 and above. I felt the data

3 looked reasonably safe, but I was not comfortable with

4 the hemoptysis risk in children, and I feel that needs

5 more investigation.

6   DR. JACOBY: Dr. Wagener?

7   DR. WAGENER: Jeff Wagener. I voted no,

8 partly for the reason that Dr. Castile made related to

9 hemoptysis, but also I feel in reviewing the animal

10 data there was some evidence of lung inflammation, and

11 they need to do interlongitudinal -- a more -- a longer

12 term study looking at inflammation as a potential

13 adverse effect.

14   DR. JACOBY: Dr. Harkins?

15   DR. HARKINS: Michelle Harkins. I voted no,

16 solely for the pediatric signal in hemoptysis, and I

17 think it should be monitored longer term to see if it

18 has any other ill effects. But I wouldn't have a

19 problem with it in the adult population.

20   DR. JACOBY: Dr. Connett?

21   DR. CONNETT: This is John Connett. I voted

22 no on the basis of the hemoptysis data. But it seemed

1 to me to be concentrated in the patients that had the

2 really low lung function, not necessarily pediatric.

3   DR. JACOBY: Dr. Stone?

4   DR. STONE: Kelly Stone. I voted no. The

5 data presented didn't meet the safety standard, again,

6 particularly in children.

7   DR. JACOBY: Dr. Blake?

8   DR. BLAKE: Kathryn Blake. I also voted no,

9 and it was primarily because of the pediatric risks

10 that were identified, and that this is a new drug

11 class, and I feel like that for children we have to be

12 especially careful.

13   DR. JACOBY: David Jacoby. I voted no for

14 reasons that have already been stated by others.

15   DR. TERRY: Peter Terry. I voted no for the

16 reason I felt there was insufficient evidence to make

17 any comments about safety.

18   DR. JACOBY: Dr. Greenberger?

19   DR. GREENBERGER: I voted yes. I thought

20 there was sufficient weight of evidence to understand

21 the safety profile, and specifically regarding the

22 hemoptysis that was not life-threatening or life

1 endangering. And that would be a manageable risk for

2 which the physicians would no longer prescribe the

3 medicine, and the ones who could be on the treatment

4 would continue.

5   DR. JACOBY: Mr. Mullins?

6   MR. MULLINS: Rodney Mullins. My vote was

7 based upon concerns with the high level of -- the lack

8 of tolerability and the dropout rate. And I was

9 looking for some understanding about those that dropped

10 out, further analysis, and just the overall -- the high

11 occurrence of hemoptysis, even in adults, concerned me.

12 Thank you.

13   DR. JACOBY: Dr. Tracy?

14   DR. TRACY: Jim Tracy, and I voted yes. I

15 thought there was sufficient evidence, looking at the

16 regulatory requirements. I do understand the concerns

17 with pediatric. I think that that is -- needs to be

18 watched carefully down the road.

19   DR. JACOBY: And Dr. Herring?

20   DR. HERRING: Amy Herring. I also voted yes.

21 While I do have concerns about the children, to me the

22 overall profile didn't include any clearly irreversible

1 adverse events, and given the disease area. That's my

2 vote.

3   DR. JACOBY: The final voting question is

4 Question 6. Do the efficacy and safety data provide

5 substantial evidence to support the approval of DPM at

6 a dose of 400 milligrams twice daily for management of

7 cystic fibrosis in patients aged six years and older to

8 improve pulmonary function? If not, what further data

9 should be obtained?

10   So this is really a combination of the

11 previous two questions. Any comments on this?

12   (No response.)

13 Okay. Then, go ahead and vote.

14   (Pause.)

15 Okay. Everyone has voted.

16   DR. HONG: Okay. We have zero yeses, 14 nos,

17 and zero abstains.

18   DR. JACOBY: Okay. Let's start back over

19 here. Dr. Herring?

20   DR. HERRING: Amy Herring. I voted no for

21 the reasons previously stated.

22   DR. JACOBY: Dr. Tracy?

1   DR. TRACY: I voted no principally for the

2 efficacy component.

3   DR. JACOBY: Mr. Mullins?

4   MR. MULLINS: I voted no, particularly

5 because the data was striking to me as it occurred in

6 the areas of safety. I mean, they were very clear, and

7 then, as far as efficacy, the -- much of the data was

8 statistically insignificant. And then, once again, the

9 post-marketing analysis, once it went out to the real

10 world in Argentina and other places in South America.

11   Thank you.

12   DR. JACOBY: Dr. Greenberger?

13   DR. GREENBERGER: I voted no. I stated

14 earlier that I voted no, because the efficacy -- there

15 was not substantial evidence based on the framework we

16 were given for improvement in pulmonary function.

17   I would also like to raise a possibility

18 regarding further data, that using hindsight Study

19 2002, with the dose-response study, was -- gave

20 misleading results as choosing the dose, led to too

21 high of a dose, and that the long-term benefit, if the

22 sensitivity analysis can be accepted, actually shows

1 benefit with lower dosages than the supposed 400

2 milligram BID.

3   DR. JACOBY: Dr. Terry?

4   DR. TERRY: Peter Terry. I voted no for the

5 same reasons I voted no in Questions 4 and 5.

6   DR. JACOBY: David Jacoby. I voted no for

7 the reasons that I voted no on the other two questions.

8   Dr. Blake?

9   DR. BLAKE: Kathryn Blake. I voted no,

10 primarily because of the pediatric efficacy and safety

11 data. But I would support a sponsor's submission for

12 adult use only. I was very moved by the stories from

13 the patients and their clinicians, and I feel like this

14 does have a place in the treatment of adults.

15   DR. JACOBY: Dr. Stone?

16   DR. STONE: Kelly Stone. I voted no for the

17 reasons previously stated.

18   DR. JACOBY: Dr. Connett?

19   DR. CONNETT: I voted no, because I voted no

20 on the previous two questions. But I think it was the

21 quality of the data in especially the first study, not

22 especially good, and the safety issues.

 1   On the other hand, I wish I could have voted

 2   yes, because it seems like some kind of treatment that

 3   does what this drug is intended to do is needed.

 4   DR. JACOBY: Dr. Harkins?

 5   DR. HAWKINS: Michelle Harkins. I voted no,

 6   because I had a split vote, so, therefore, I had to

 7   vote no. But I do feel that it is an unmet need. I

 8   feel very confident in the adult population, and that's

 9   all I have to say.

10   DR. JACOBY: Dr. Wagener?

11   DR. WAGENER: Jeff Wagener. I voted no. I

12   feel that if it was just for adults it would be more

13   reasonably approved. But I feel they need more

14   information, more study in children, particularly long-

15   term, looking at exacerbations and other outcomes

16   besides just FEV1.

17   DR. JACOBY: Dr. Parad?

18   DR. PARAD: This is Richard Parad. I also

19   was forced to say no by my prior answers and my concern

20   about risk/benefit ratio in children, but would have

21   voted more positively for adults.

22   DR. JACOBY: Dr. Castile?

1   DR. CASTILE: Bob Castile. I voted no,

2 because I thought there was a real lack of clarity in

3 both the risk and the benefit data, which didn't permit

4 me to really adequately assess the risk/benefit ratio,

5 and particularly over the range of the population

6 stated in the question. And so I think this is

7 unfortunate, because I do think it has a role, but

8 based on the data presented and the question asked, I

9 had to vote no.

10   DR. JACOBY: And Dr. Cataletto?

11   DR. CATALETTO: Mary Cataletto. I voted no.

12 Again, with my colleagues, I wish I could have voted

13 yes, because I think there is a place for a drug like

14 this. But I think that further studies are necessary.

15 Adjournment

16   DR. JACOBY: Okay. Those are all of the

17 questions we have been asked to consider.

18   I would like to thank the members of the

19 Committee. I would like to thank the people who did

20 presentations on behalf of the sponsors. I would like

21 to thank the FDA, and I'd like to thank all of the

22 people who participated in the open forum.

1   Thank you, all.

2   Dr. Durmowicz?

3   DR. DURMOWICZ: I would also join in from the

4 FDA standpoint and thank everybody for coming here and

5 sharing their views, and I thank the patients and

6 advocates for coming as well.

7   (Whereupon, at 3:23 p.m., the meeting of the

8   Pulmonary-Allergy Drugs Advisory Committee

9   was adjourned.)

10

11

12

13

14

15

16

17

18

19

20

21

22

347

1   CERTIFICATE OF NOTARY PUBLIC

2   I, NATALIA THOMAS, the officer before whom the

3 foregoing hearing was taken, do hereby certify that the

4 testimony appearing in the foregoing pages was recorded

5 by me and thereafter reduced to typewriting under my

6 direction; that said transcription is a true record of

7 the testimony given by said parties; that I am neither

8 counsel for, related to, nor employed by any of the

9 parties to the action in which this hearing was taken;

10 and, further, that I am not a relative or employee of

11 any counsel or attorney employed by the parties hereto,

12 nor financially or otherwise interested in the outcome

13 of this action.

14

15

16

17

                     _____
18   NATALIA THOMAS
                     Notary Public in and for the
19   State of Maryland

20

21

22

348

1   CERTIFICATE OF TRANSCRIPTION

2   I, LISA SIKES, hereby certify that I am not the

3 Court Reporter who reported the following proceeding

4 and that I have typed the transcript of this proceeding

5 using the Court Reporter's notes and recordings. The

6 foregoing/attached transcript is a true, correct and

7 complete transcription of said proceeding.

8

9

10

11

_____   _____
12 Date   LISA SIKES
                                  Transcriptionist
13

14

15

16

17

18

19

20

21

22

0

0.0498 165:22

0.05 165:20

0.059 195:3

0.8 197:20

001 51:6

1

1 165:19 166:3
 209:13 273:10

1,000 37:16 258:15

1,150 243:11

1,350 56:18

1.4 114:14

1.57 158:14

1.7 73:16

1.9 76:22

10 27:9 45:20
 47:11 77:18 78:3
 99:6,11,12,18,22
 100:2
 102:12,13,18
 103:1 104:4
 133:19 134:9
 155:2 156:7
 161:1 199:12
 202:4 204:7
 225:17 229:22
 245:15 246:1
 250:10 259:17
 283:12 312:13

10.4 133:12 296:11

10:48 151:10

100 58:22 149:2
 173:3,22
 177:10,16
 187:6,9,11,14
 188:7 192:14
 210:3,11
 211:4,6,13 226:2
 309:22 327:5

101 58:16

107 190:1

10903 1:16

10K 247:8

10-minute 151:9

11 108:6 147:3
 150:5 177:20
 198:7 203:10
 325:1 331:11
 336:22

11.4 70:21

110 83:13

112 50:6

113 49:22

118 49:20 159:13

119 84:14

11-year-olds 147:7
 205:5

12 61:5 77:18 78:2
 101:6 102:13
 103:16 108:6
 118:8,14 147:3
 157:5 203:10
 243:8

12:36 212:6

120 83:13 95:7,8
 157:19 306:2
 329:1

121 62:15 159:16

13 62:21 132:2
 314:6

139 46:5

14 47:13 53:6
 62:11 113:15
 160:4 210:18
 229:7 341:16

142 84:19

15 91:1 99:5 101:3
 115:5 155:12
 190:1 194:8

198:8 232:4

150 57:3 211:13

153 139:2

155 15:7

159 49:22

16 77:13 104:17
 318:4

16.7 73:14

160 95:9

165 15:12

17 31:21 71:10,14
 76:20 77:8,14
 78:19 81:7
 133:10 147:3
 177:8,11,19
 180:3 192:8
 197:15 203:10
 319:21

177 49:19 159:13

17-year 76:21

17-year-old 193:9

17-year-olds 71:16
 78:3 139:1 299:4
 318:5 321:3
 323:2

18 12:4 23:10,14
 24:4 49:20 67:15
 71:11 76:20
 107:11 147:3
 177:9,11,20
 180:4 192:3
 202:7 258:14
 314:14 316:18
 335:13 338:2

180 68:8 221:7

183 16:7

184 62:15 159:15

18-year-olds 320:5

19 197:16 202:3
 230:17 233:19

191 16:14

1972 23:1

1980 240:21

1983 218:8,11

1990s 84:13
 316:21

1998 263:22
 264:15

2

2.2 73:15 197:19
 297:14

2.5 73:21

2.6 77:5

20 33:22 55:5,11
 56:1 64:15 72:12
 81:20 94:10,19
 95:11 101:8,15
 102:10,17,18
 103:1
 105:3,7,11,13
 114:11,15
 115:2,17
 132:11,20
 166:15 218:14
 226:12 246:5
 281:3 327:13,17
 328:11

20,000 328:6

200 177:11 187:15
 211:13

2002 342:19

2004 155:8

2005 155:10 209:2

2005/2006 208:13

2006 155:11,12

2009 245:5

201 44:22

2010 156:8

2011 84:20

2012 246:14

2013 1:11 218:16

202 29:1 45:1
  157:5
  158:3,10,18
  161:3

202049 1:9

2020494 24:11

203 45:4
  117:5,12,17

204 229:21

208 23:10,15 24:5

20993 1:17

21 87:22 105:6
  314:13

21.1 73:13

211 16:16

217 16:18

22 155:8 218:7
  243:11 315:1
  325:1

23 12:7

24 58:21 62:20

240 68:12 157:19
  327:3

25 64:19 96:16
  98:10 132:1
  300:21 314:5

25.6 72:14 95:18

250 309:21

255 16:21

259 202:8

25-year-old
  230:17

26 12:11 29:14
  47:11,14,15
  48:16 55:15 56:3
  57:9,20 58:20
  59:5 61:21 63:21

64:8 90:9 115:11
116:5 117:14
119:4,7,13 145:7
159:5,18 160:4
164:6,20 174:1
176:20 249:7
284:15 288:5,14

26-week 29:16
  47:22 51:5 59:15
  78:8 160:5
  167:13 176:18
  178:17,19
  191:13,18
  193:21 196:14
  249:18

27 49:11 50:6,9
  160:21 193:20

272 49:7

28 46:6 187:7
  210:16 324:20
  325:2

29 139:3

295 49:7,17 159:11

297 62:10

───────
3
───────

3 319:18

3.9 76:13

3:01 328:15

3:23 346:7

30 1:11 33:11
  46:13 97:19 99:4
  132:11 160:11
  214:7 218:6,14
  222:13 223:4
  247:4 273:11
  276:16

30,000 28:12 37:16
  233:9

300 29:15 118:4,20
  224:13

301 29:11,19 30:6

44:5 49:19 51:3
59:3 63:1,6,12
64:5,11 83:21
107:11 109:12
141:3 142:19
145:21 149:8
159:2,11 160:11
162:2 163:22
164:4,7,9,13
166:1,15
167:11,16,19
168:10,11 170:5
171:15 174:4
176:7,17 177:7
178:2,12,15
179:5,22 181:7
186:1,8 188:4
189:13,16,21
190:4,5 191:6
192:9,11,18
193:6,12,19
195:19 196:14
205:17,21 206:6
209:11 210:10
320:17 334:19
335:6

301/302 136:7
  326:20

302 29:12,20 44:6
  45:6 46:14 61:20
  63:5,13 64:10
  65:2 111:6 137:1
  138:18,19
  139:1,3,9
  141:3,22 142:16
  149:6 159:3,14
  160:5,6,12
  162:1,9 163:22
  164:4,7,8,11
  166:4,17
  167:13,16
  168:11,16 172:1
  174:14 176:19
  178:5,13,15,18
  180:6 186:8
  187:22 188:2

189:14 190:7
191:7 192:10,12
193:3 194:22
195:1,20 196:15
205:18 211:1
250:3,15 272:19
273:17 335:6

305 62:10,14
  159:14

30-minute 91:1

31 1:15 87:22
  218:6 222:5

318 62:13

324 49:15

32-year-old
  223:15 240:8
  244:6

33 13:4,8

335 67:22

34 61:11

341 62:11

35 61:8 187:7
  210:14 211:8

351 17:5

36 193:20

360 309:21

361 68:7

37 13:13

370 68:10

378 49:10

38 37:20 158:1
  214:22 233:11

39 168:15

───────
4
───────

4 114:15 330:16
  343:5

4.1 62:12

4:00 90:21

40 29:9 33:17
   35:12 45:3,15,21
   46:13 66:9,17
   75:11 79:9
   137:19 157:7,19
   158:12,13,17
   159:11 160:11
   201:18 219:8
   222:19 223:16
   226:7 279:12
   312:1,9,10
   335:14

400 27:8 29:7 34:2
   35:13 36:3 44:1
   45:3,16,18
   47:10,17 49:13
   93:11,19 94:8,14
   95:5,12 96:18
   122:11 146:10
   149:7 155:1
   157:16 158:5,11
   159:5,8 196:7
   204:5 250:5
   256:10,22
   257:14 258:5
   307:7 309:15
   330:19 341:6
   343:1

40-year-old
   144:15

41 198:7 230:2

420 44:22

43 192:2 202:7
   247:7 316:17

44 13:19

440 131:21

45 211:8

45,000 328:10

450 56:14 57:7

47 50:5

48 29:4 68:12
   157:14 243:12

49 126:13 195:4
   222:17

———————
5
———————
5 257:5 336:12
   343:5

5.4 74:19 76:11

5.7 72:11 77:6
   95:17

50 29:8 30:18
   45:10,22 47:10
   77:17 113:18,20
   137:10,17
   158:20 159:6,9
   173:22 186:6
   187:15 188:7
   206:2 224:22
   283:2 293:10,11
   312:5,10,13
   327:9,11

50/50 99:19

501(c)(3 214:16

52 161:5

52-week 145:8

53 97:18 159:14

54 83:14 142:11
   168:10,17

55 56:16

56 233:5,14 243:8

59 58:20 194:5

———————
6
———————
6 47:13 341:4

6.3 70:21

6.7 53:8

6.8 309:11

60 58:5 89:16
   173:4 186:6
   200:3 249:15
   320:18

600 93:13 98:8,21
   104:17 161:7
   202:8 235:5

62 171:17

63 195:4

635 34:12 98:17

64 167:10 178:15

65 139:6 172:2

68 85:9 160:22

69 14:7

———————
7
———————
7.1 49:13

7.6 133:14 296:11

7.8 76:22

7.9 76:13

70 279:12 283:2

71 58:20

71.7 53:7

713 67:22

719 160:18

73 167:11 178:16

731 160:17 161:6

74 98:7

75 38:6 152:20
   173:4,22

———————
8
———————
8 210:11

80 30:18 119:19
   139:9 144:14
   186:7 327:6,14

82 14:12 161:8

83 51:4 83:14
   167:12 168:10
   171:21 178:18
   179:7 194:5
   206:3

86 50:7

88 167:12 178:18

———————
9
———————
9 246:14

9.4 74:18 76:10
   309:10

90 38:7 46:13
   148:2 157:7
   269:15 319:8
   329:3 335:14

90s 84:19 314:15

92 52:16

92.2 50:3

94 14:17

95 161:14
   168:13,18
   189:22 192:6
   194:6

96 243:11

97.4 62:19

99 58:15 329:7

———————
A
———————
a.m 90:22

AA-2 249:4

AA-4 250:2

ability 70:9 194:15
   311:7

able 30:7 31:11
   104:10 122:19
   125:17 132:22
   141:1 152:2
   160:22 197:6
   208:18 219:4
   223:20 226:16
   227:18,19
   228:3,7 239:18
   240:18 244:9,10
   245:14,19
   247:7,9,12,18

249:8 250:12 284:12 285:1 288:19 289:20 311:16

abnormal 216:17 298:13

abnormalities 28:7,11 69:6

absence 318:19

absolute 29:16 144:17 147:11 159:18 164:20 191:17 206:4 208:21 211:13 334:22

absolutely 96:3 127:14,17,20 128:1,5 147:6 286:10 310:7 322:10

abstains 331:12 337:1 341:17

academic 264:2

accelerated 247:16

accept 335:8

acceptability 41:14

acceptable 31:20 45:21 90:1 92:9 134:10 252:16 255:12 268:3 281:15 293:21

accepted 48:1 91:21 261:5 342:22

accepting 165:6 282:14

access 276:21 289:20

accommodate 126:2 243:2

accompany 237:20

accomplish 79:16

accordingly 33:13

account 58:8 89:4 125:15 128:16 146:18 147:8 158:18 161:17 262:15 293:8,22 295:16 322:5 337:15

accounted 53:19

accounting 38:6 77:5 147:1 185:14

accounts 172:6 202:7

accredited 152:13

accumulate 55:11

accuracy 170:6

accurate 75:22 178:22

accurately 31:12 206:12

achieve 93:22

achieved 172:20 173:12,21 174:16 190:3 195:6

achieving 192:19

Achromobacter 223:1

acknowledge 60:3 91:13 126:15 132:7 327:10

acknowledged 54:6 156:10

across 29:16 69:20 71:9 111:13 119:6 122:18 138:10 159:18 161:12 164:20

176:18 181:14 185:5 194:16 217:6 219:11 229:21 286:15 308:15 326:22

act 22:8 23:1 34:13 37:4 156:2

acting 25:7 101:3

action 60:10 65:21 67:7 71:22 120:10 286:15 323:20 347:9,13

actions 43:4

active 68:18 80:21 146:7 159:8 183:7,13 184:14 187:7 188:9 210:15,20 237:21

actively 69:13 196:15 210:5

activities 37:5 80:2,7,17 81:11 246:22

activity 284:16

actual 82:7 128:17 288:4 315:18

actually 42:4,5 94:21 98:7 99:10 101:7,15 102:1 103:6 109:1 113:16 114:2,7 117:11,22 118:11 119:10,14,15 125:18 127:5 136:4,11 137:2 141:12 144:7,21 147:15 148:15 151:2 182:18 186:15 218:7 221:22 224:15 226:1,3,6 227:4

229:18 243:6 245:17,20 246:7 258:12 259:4 266:20 277:12 283:7,17 287:1 288:18 289:16,19 292:9 295:12 299:11 300:8 310:5 313:19 315:4 320:11 322:6 324:21 326:12 329:12 342:22

actuated 35:14

acute 82:9 204:9 317:22

acutely 60:14 109:7

add 42:12 43:7 121:18 144:3 268:20 283:14

added 41:1 42:14 130:3 242:6 281:5 325:3

adding 90:16 238:18 281:10 282:5

addition 36:17 42:2 47:17 69:11 79:8 89:14 122:19 193:14 199:10 221:4 238:22 281:4

additional 42:11 43:7 68:8 86:8,18 98:5 156:5 160:21 161:5,9 162:17 163:14 172:5 189:19 190:2 194:8 197:7 204:1,17 298:17 336:1

additive 33:22

118:1 120:9

address 32:20
36:18,20 44:11
51:22 53:20
69:3,18 81:9
82:22 86:19
92:12 147:13
213:11 217:17
226:16 228:3,19
229:4 248:18

addressed 116:12
149:10 292:14

addresses 40:19
261:15

adds 235:15

adequacy 156:12

adequate 60:21
123:17 136:18
253:2 254:9,19
255:22 284:22

adequately 129:15
284:3 345:4

adherence 43:10
79:16 90:14
181:2
230:9,13,14,18,1
9,20 232:9
236:21
237:4,9,22
238:20

adherent 108:4
237:1,2

adjourned 346:9

Adjournment 17:5
345:15

adjust 175:17

adjusted 209:13
325:3

administer 239:20

administered
35:13 155:3

196:10

administration 1:1
22:20 32:5 36:3
47:2 81:4 94:8
101:4 103:11
113:12,17 114:1
161:2 164:13
199:22

admire 261:3

admissions 328:6

admit 253:10
313:21

admitted 215:13

adolescence
230:15

adolescent
135:13,17
237:21 314:7

adolescents
89:1,19 120:20
135:11 136:6,11
137:1 138:21
139:9 140:20
141:2 143:9
145:3 231:8
250:14 254:10
256:17 315:2
319:9,21
320:12,19 321:5
332:4

adult 19:14 42:16
71:14,17 82:9
92:2 131:10
132:21 133:11
147:12 177:15
178:7,9 224:12
229:6,12,19
235:3 236:2
237:21 260:1
261:5 279:20,21
280:1,4 293:11
303:11 320:20
338:19 343:12

344:8

adulthood 230:15
335:22

adults 71:11 77:10
89:4 108:7
120:21 135:11
136:7,12 141:2
143:10 144:12
147:9,20 149:9
193:5 203:5
216:3 224:13
225:1 228:1
229:21 234:14
254:10 259:22
264:22
267:13,16
279:13,20 296:4
299:12
300:1,19,20
304:13,18
305:17 315:2
320:12 322:6
333:14,15
334:20 340:11
343:14
344:12,21

advance 152:4

advanced 131:9

advances 28:14
37:18 241:8

advantage 232:11

adverse 31:17
49:17 50:13
52:14 63:3
69:18,19
70:2,7,10,13,15,
18,20
71:1,9,13,15,18,
20,21 72:1,16
74:17
75:3,7,9,15,17,1
9
76:1,4,6,10,16,2
1 77:5,17 78:2
79:14 81:2,5,6

86:20 90:2
103:2,22 104:2
106:11 109:13
124:6,18 130:21
133:17 167:20
188:22 189:1
196:17,19
197:1,8,13
198:5,9,13
199:19 200:6,7,8
201:4,20,22
202:2,10,13
203:7
204:3,12,13,17
205:1,10
206:21,22 262:5
294:4 297:9,10
298:11 306:5
307:21,22 313:2
338:13 341:1

advise 25:20
32:11,18 140:4
213:1,9

advised 141:8

advisory 1:5 2:5,9
3:3 4:3 5:3
18:12,14 20:9,16
22:7,9,22 23:1
26:11 32:7 33:6
152:16 229:4,9
232:12 235:6
255:21 346:8

advocacy 214:18

advocate 221:17
258:17

advocates 3:16
20:17 346:6

advocating 234:4

aerosol 85:4 88:19
90:5

aerosolized 84:17

aeruginosa 162:4
222:7 223:3,16

AEs 99:20,22 100:1

Affairs 13:9 33:3

affect 265:2

affected 38:5

affecting 37:15 241:2

affects 241:1

affiliation 233:2

afternoon 205:16 207:10 220:7 233:1 234:21 240:2

against 130:10 310:13,14,21 322:11 332:15,18

age 24:14 31:21 33:9 40:14 50:17 66:6,19,21,22 67:5,15 68:2 71:9,10,11,14,18 74:14 77:3,8,14 78:19 81:7 99:7 104:17 108:6 132:2 133:7 137:15 144:10,20 147:1 148:16 149:5 150:5,12 154:22 157:6 161:14 177:3,9,10,15 178:2,3,8,10 180:3,4,5 192:3,9 203:3,9,15 204:14 216:2 222:4 230:17 231:6 233:13 250:22 257:16 260:4 300:3 301:6,12,17,20 314:3,6,7,14 316:15,18 317:4

319:21 325:2 334:7 335:13

aged 341:7

agencies 23:5

agency 213:16 263:21

agency's 23:18

agenda 12:2 13:3 14:3 15:3 16:3 17:3 24:10,18 25:14

agent 28:1 31:1 34:13 154:8 199:6 216:8 283:15

agents 27:18 154:6 237:11

ages 76:19 269:20

aggravated 71:4,7 197:15

aggressive 225:3

ago 143:12 215:1 233:17 287:13

agreed 58:10 188:1

agreement 337:13

ahead 106:3 121:14 227:19 228:7 241:15 341:13

Ahmet 235:2

air 216:10,11,13

airway 27:14 28:9 34:13,15,16 35:6 39:3,4,8,17 40:7,12,17 41:2 42:17 43:22 60:11 61:16 64:13 82:17 88:19 92:2 105:20 106:6

112:19,20 190:14 219:13,14 225:10,12,16 226:16 228:3,19 231:15,16 235:8 238:10,16 239:11 302:20 303:15 305:15,18 313:3 323:21

airways 82:18 97:13 116:7 216:14 245:9 246:17 302:14

aisle 254:6

Aitken 220:7,9 224:7

al 118:7 229:19 230:12

Albuquerque 7:17

albuterol 47:1 100:7 101:5,9 103:12 105:22 113:4 115:2 139:16,18 140:7

alcohol 27:2

alert 79:1

Alex 214:22 215:2,7,8,15

alike 216:5

alive 218:19

Allergic 19:21

allergist/ immunologist 19:20

allergy 4:7,9 5:9,13,14 9:9 10:7 12:12 18:20 20:19 21:16 152:10 264:4

allergy/

rheumatology 21:14

Allergy-Immunology 2:19 20:13

allocation 75:1

allotted 214:5

allow 80:8 219:19 226:15 228:18 241:8 264:14

allowable 68:21 160:10

allowed 22:5 46:15,17 54:17 87:3 129:15 241:11 292:18 335:11

allowing 33:22

allows 35:3

alluded 115:6 117:5

alluding 121:17

alone 44:11 118:12,13 194:3 209:16 236:6

alpha 41:21

already 18:7 25:14 27:1 37:9 42:12 51:12 57:13 72:19 80:16 86:16 90:17 92:8,16 105:20 121:1 146:6 149:1,10 156:22 184:8 208:7 238:14 251:22 283:3 289:17 300:6 320:10 339:14

alternating 222:11

alternative 183:20

246:17

altogether 183:19

alum 240:11

am 18:11
19:6,10,16 33:2
42:19 65:16
67:18 81:17
104:15,16
147:15 151:17
152:11 162:21
174:22 177:2
210:1,6
214:14,22
217:16 220:9,10
223:22 224:15
229:11
233:2,4,5,12
234:4 235:2
240:3,10,19,20
241:6 243:19,20
244:9,10 246:5
247:9,12 251:17
256:1 261:12
262:13 275:4
276:13
277:15,16
298:14 303:11
335:10 347:7,10
348:2

ambiguous 181:12

America 111:6
138:5,7 289:9
307:3,10,13
342:10

American 91:21
143:16 275:19
277:6 291:11
294:22 307:1
311:3

among 96:17,19
212:9 236:4
237:22 238:21
332:3

amount 58:18 74:9

84:1 88:12
130:6,9 244:19
266:6 295:22
299:11,14

amounts 31:2
74:11 118:8
181:13

amplify 130:19

Amy 8:5 20:21
331:16 340:20
341:20

analyses
30:7,11,16
44:6,14 48:11
49:4 53:15 55:20
115:21 116:1
156:10,11,14
162:16 170:9,12
183:16,21
184:6,17
185:13,22 186:7
189:15 194:1,4
195:3 205:17,20
206:2 272:11
278:14 288:5
320:4

analysis 31:10
48:16,19,20,21
49:1,7 50:1,2,22
52:17 53:2,14,20
54:10,12,17,19
55:13,14 57:19
59:13 61:8
62:3,10,18
64:2,5 84:1,6
90:7 116:13
122:17 124:3
129:4,12
141:6,9,12,14
142:21 143:1
158:8 162:9
163:11,14,15
165:3,8,16,21
166:10,22
167:3,5,22

168:6,20
169:1,3,14
170:8,11,15
171:3,9,18,22
172:3,4,8,10,11
174:2,4,11,20
175:12,17
176:16 177:2,5
178:12 179:3,6,8
180:9,21
181:1,5,9,13
182:11 183:18
184:1,11,20
185:8,10,12,20,2
2 186:6
189:9,19,20
190:2,4,9 193:22
209:22 252:8
263:20 274:18
275:17 278:12
285:18 288:1
289:1,2,9 291:1
294:7,17 298:8
325:1,4,7,8,9
326:9 327:7
332:19,20
340:10 342:9,22

analyzed 48:13
54:20 57:8 80:4
167:7

ANCOVA 57:19
64:8 176:20

and/or 38:16

Andy 117:17

anecdotally 96:21
110:7,14 131:8
315:4 337:18

anecdotes 336:8

animal 301:3
338:9

annual 151:3

anomalous 307:4

answer 100:7,9

104:8 108:13
109:3 268:17
280:15 291:9
335:4 337:19

answered 209:18
330:15

answering 92:22
181:17

answers 248:22
344:19

Anthony 10:12
12:11 16:21 26:2
251:15

antibiotic 48:8
50:19 61:5,12
63:9 64:19 84:17
175:8 176:9
191:10

antibiotics 39:22
41:21 64:15
84:22 85:4 111:1
220:19 223:3,19
225:3,4,5,14
247:16 301:8
318:14 328:7,9

anti-filibuster
151:18

ANVOCA 57:9

anxious 22:13

anybody 114:10
265:14

anyone 152:4
212:9 281:16

anything 125:15
137:7 212:2
267:1 269:22
281:22 282:3
287:6 305:22
325:22

anywhere 286:19
292:12

apart 65:12

138:11 211:4 319:5

apologize 152:4 308:9

app 150:13

apparent 68:13 112:5 124:16

appear 88:2 90:3 135:14 177:14 180:2 210:19

appearing 347:4

appears 30:12 71:7 73:7 74:1 78:15,18 83:18 85:10 87:1,9 92:9 136:13 195:18

apples 290:14

apples-to-oranges 194:14 206:9

applicable 65:8,22 320:19

applicant 26:18 164:10 165:3 170:13 176:2 179:18,19 183:21 188:1 257:18

applicant's 163:21 179:15

application 24:11 45:8 53:21 152:21 155:7 162:19,22

applied 55:8 166:5 278:13

apply 286:15

applying 57:2 62:22

appreciate 33:4 37:6 229:10

248:12 276:17 304:12

appreciated 142:21

approach 58:9,12 59:5,10 63:20 119:17 127:1 128:13 129:9 132:19,20 171:5 334:18

approaches 54:1 125:5 126:1 132:16 281:21

appropriate 80:12 93:17 96:13 132:22 172:13 180:18 238:1,19 252:16 253:14 265:8,10,11 268:2 273:5 290:12 292:6

approval 80:7 81:11 156:4 194:19 254:8 257:8,14 333:10 336:14 337:10 341:5

approve 254:18 255:13 278:9 287:16 334:7

approved 27:12,22 28:16,17 34:2 40:18,20 46:14 84:11 153:17,22 246:12 248:7 258:19 259:4,7 262:2 265:4,7 287:13,15,18 305:19 344:13

approving 224:16 228:10 264:14 287:17

approximately 28:12 29:4,15

30:18 36:4 37:20 173:4 181:13

arbitrary 59:8 152:5 186:14

area 163:5 215:4,18 225:16 226:16 228:19 285:3 341:1

areas 201:21 302:15 304:20 342:6

aren't 135:15 241:14 265:4 287:5

Argentina 138:8,17,22 139:4,8 157:6 159:15 289:9 306:14 307:6,9,12,16 308:3,5,8,11 342:10

Argentinian 138:11 272:14 308:15

argue 134:9 224:1 282:5 320:7 322:19

argument 183:2

aridol 27:12 34:7,9,11 93:19 97:13 115:3 140:8 154:15,17

Arizona 240:11

arm 50:13,14 52:12 53:7,8 57:2,6 59:3 63:4 64:22 65:6 70:13,14 107:2 127:6 136:16 146:7 157:18 158:5 200:22 298:4

armamentarium 235:14

arms 50:16 52:22 69:21 76:18 87:22 132:10 135:20 136:15

arrive 41:11

arrows 220:20

artificially 176:5

asked-for 257:17

asli 303:7

aspect 88:8 242:22 254:8 264:20 271:8

assertion 126:13

assess 27:14 30:7 36:13 54:11 58:9 80:3,9 125:7 194:15 345:4

assesses 109:7

assessment 80:5 154:16 205:14

assessments 277:4

assign 184:2

assignment 169:22

Assistance 9:6

associate 7:13 8:13 19:13 20:18 224:10

associated 28:8 38:8 48:2 72:1,16 74:5 76:12 78:5,18 79:14 87:14 88:6 100:3 131:8 163:9 169:19 198:13 199:20 204:3 230:21 231:1 296:15 318:12

Associates 9:9

association 73:2

assume 94:13 210:6 331:4

assumes 52:3 57:11 58:13 125:18

assuming 57:21 128:13 259:16

assumption 102:4 126:20 169:14 171:8 175:21

assumptions 126:5 168:2,3 169:22 170:17,19 187:3

asthma 9:9 35:1 105:21 106:20 107:3 264:6

Asthmatic 106:19

asymptomatic 105:10

Atlanta 20:15

attack 247:10

attendance 213:7

attendees 26:5 251:11

attention 31:22 92:18,21 188:10 207:16 224:6 225:9 238:1 248:17

attorney 347:11

attractive 83:6 121:5

attributable 186:2 187:13

attributed 69:8

audience 248:16

August 247:8

aureus 222:7

223:2,17

Aurora 9:15

Australasia 138:6

Australia 34:4 106:14 138:7 159:12 308:1 316:4

Australian 140:13 308:9

author 264:3

authority 22:22

authorized 23:15

automatically 148:4

autosomal 28:4 37:11

available 40:13 41:7 54:9 57:14 59:7 61:2 80:15 98:2 153:18 175:16 181:14 217:5,15,18 235:11 241:5 242:2 306:19,20 307:1 313:1,6

Avenue 1:16

average 41:19 50:17 53:6,8 57:15 64:1 89:9 100:21 127:4 161:14 168:8,14 169:9 181:14 184:17 185:4 243:10 288:16

avium 222:8

avoid 132:19

await 234:16

awaken 90:21

aware 22:12 28:4 54:2 122:12 276:12

awareness 214:18

away 30:2 36:1 118:21 133:11 236:15 245:14 278:21 279:3 290:15 334:5

awesome 219:15 245:11

awful 233:10

axis 118:10 173:5

aztreonam 222:11

———————
B
———————

baby 218:9

background 36:7 37:7 223:15

backwards 145:12

bacteria 42:6 82:19 247:14

bacterial 39:9,11

bad 96:16 97:2,4 184:22 267:13

Badrul 10:5 21:15

balance 238:20 304:12 322:10

balanced 50:15 63:6

ballot 330:6

Baltimore 4:16 9:21 224:11

bar 114:22 115:3 253:18 255:14 263:14 268:12

barely 272:20

barriers 90:14

bars 230:2

base 194:19

based 24:18 29:9 32:15 44:7,10

48:6,15 50:3,18 52:18 53:14 54:19 59:18 62:19 63:20 64:1 65:11 66:7 67:12 71:19 79:5 80:10 85:7 104:7,10 105:20 118:7 125:3 126:17 127:12 129:16 133:7 141:4,6 145:21 146:1,19 158:17 171:16 192:9 226:4 231:21 237:11 238:3 250:6 254:9 258:19 260:19 273:4 285:20 287:2 300:6,9 312:10 326:19,20 327:3,7 332:16,17 333:2 340:7 342:15 345:8

baseline 47:9,21 48:15 51:2,14 52:8 53:6,22 55:2 57:10,12,20,22 61:21 65:5 66:8 75:8 83:12 111:20 123:16 126:21 127:2 128:11 140:22 142:3,5,9 143:3 145:17 149:11 158:9 160:11 161:11,22 162:4 164:16,20 168:10 171:4 173:13 174:1 178:21 184:20,21 185:7,15 189:20 190:8 192:13 203:13,15

211:12 249:6 250:14 285:20 286:6

basic 183:22 238:2 246:22

basically 135:5 233:19 256:8 257:17

basing 59:8 142:11

basis 29:6 45:8 151:4 244:10 277:3 288:8,9 322:22 338:22

bathroom 216:13

Beach 247:8

Beacon 247:8

bear 285:2

bears 121:11

beat 34:18 216:15 218:13

beauties 289:15

beautiful 218:9

became 68:13

become 27:20 42:1,5 231:11 305:21

becomes 116:15 230:14 271:9,22

beforehand 110:1

begin 47:20 153:3,10 163:4 166:10 188:15 189:7 251:9 261:11 329:17

beginning 32:17,21 109:20 200:18 212:22 213:9,12 303:17

begins 295:2

behalf 25:7 220:11

345:20

behaving 119:7

behind 229:12

believe 32:5 54:1 80:11 89:22 92:13 171:11 172:13 212:15 237:16 247:3 262:11,21 263:15 265:2 266:12 304:8 306:14 312:20 315:19 326:14 332:10 335:6,8 337:9

believes 32:8 212:18 262:10

bell 279:2

beneficial 174:12,18 265:11

benefit 33:18 63:16,19 66:19 86:17 89:21 118:5 121:3 134:11 136:15 185:15 195:20 205:16 209:17 227:18 231:22 237:18 253:22 254:2,12 255:12 260:9 272:17 274:18 275:19 279:10 282:13 285:11 292:4 293:17,19,21 295:13 310:17 320:5 321:20 323:22 326:7,14 331:20 332:12 336:2 342:21 343:1 345:3

benefit/risk 79:9 205:14

benefits 44:1 193:11 260:14 276:22 294:6,17

benefitted 90:9

benefitting 185:18

besides 178:1 186:9,16 226:17 344:16

best 41:11 50:20 58:9 63:10 68:14 91:8 92:8 128:6,11 181:22 210:17 236:11 241:21,22 270:8 275:18

Bethesda 4:10

better 42:9,21 82:22 97:1 107:21 108:11 111:12 128:3 136:12 137:3 139:6 148:5 149:13 170:14 184:14 185:16 187:9 190:21 191:1 216:22 227:2 242:4 264:13 273:22 274:20 281:22 291:13 306:3 307:18

beyond 80:1 209:15 261:1 279:4 289:19 295:13 305:11

bias 51:18 52:5,18 55:17 129:11 264:2 322:8

biased 167:4

biases 132:19

BID 34:2 343:2

bigger 143:16

144:21 250:21

biggest 242:5 244:18 283:17 304:17

Bilton 36:18 103:7 104:13,15,16 106:4,21 110:16 111:3 120:5,7 122:1 139:20 140:3 302:22 303:2

Biometrics 15:14 16:8 21:8

biostatistics 7:7 8:7 11:7,8 15:15 16:9 19:17 20:22

birth 231:5

bit 31:12 63:22 143:22 150:11 184:10 222:3 224:17 225:8 245:19,20 253:9 268:21 270:3 301:4 303:6 316:11 322:6 327:22

Blackberries 18:6

Blake 2:12 19:22 107:5,6 110:11,18 111:16 115:6 149:17 150:1,2 208:3,5 272:5,6 299:7,8,18 300:11,15 333:11 339:7,8 343:8,9

Blake's 122:8

bleeding 88:13,20 197:22 215:8 303:15 337:16

bless 242:10

blessed 240:19

blessing 234:11

blind 47:12 50:5
86:7

blinded 73:18
161:6 200:19

blinding 158:19

blobs 135:5,12

blood 74:9 200:3
303:7

blown 245:14

blue 53:3 136:2
141:20 142:8
146:7 166:11
173:1,15
192:17,22

board 235:6

boarded 215:13

Bob 19:3 335:20
337:11 345:1

BOCF 57:15 58:19
171:5,9,11 172:4
179:3

body 80:20
241:1,3,19
299:14

boils 31:7

book 48:22 59:11
63:15 68:17 70:6
75:21

Boomer 233:4

border 160:10

borderline 278:22
283:16 335:22

born 240:21
241:10,12

Boston 8:19,20
19:7 235:4

bottom 301:15

bounce 185:2,3

bouncing 185:6

bounds 241:15

bowling 222:20,22

box 154:18 217:5

boxed 73:9

Boyle 224:9,10
229:1

breadth 283:18

break 96:1 135:19
143:14 151:9,11
212:4,5 328:15

breakdown 75:2
230:2 232:5

breaks 22:17 91:1

breath 35:13,21
245:17

breathe 36:1
216:10,13,18

breathing 215:19
219:8 233:12,18
246:1 247:1

Brett 14:7 36:14
67:18

bride 215:4

brief 26:19 44:2
153:3 155:5
156:20 163:4,22
184:7 287:4
309:2 316:1
328:18 331:2

briefing 48:22
59:11 63:15
68:17 70:6 75:21
179:15
211:18,20

briefly 69:3 117:7
290:22 331:15

Brigham 8:17 19:8
235:4

bright 240:20

bring 99:13
216:22 222:1
264:1 272:13
297:20

bringing 120:15

brings 223:7 242:9

broad 144:10
282:22
286:15,16

broadly 184:11

broken 143:6

Brompton 104:16

bronchial 27:16
31:1 34:7,19
46:19 47:1 72:6
73:4 93:20
154:2,16

bronchiectasis
35:1

bronchitol 1:8
24:12 154:13
156:1 237:7
243:22 309:8

bronchoalveolar
301:20

bronchoconstricti
on 72:8,17,20
73:3 97:11,14
99:15,17 154:19
157:10

bronchoconstricti
ve 159:20

bronchodilator
87:8 97:9,15,19
100:12 101:3,5
115:1 156:2
190:13 199:21
208:10 209:3

bronchodilators
39:22 97:2 154:5

bronchoprovocati
on 199:6

bronchoreactivity
112:20 115:3

bronchoscopy
318:2

bronchospasm
72:3,4,15,22
73:6,8,11 86:21
87:5,9 93:14
96:10 106:9,17
108:15 109:8
140:13,16
160:19 198:15
199:7,15,20
204:9

Brook 6:18,19
19:2

brother 240:12

brought 254:4

Bruce 236:21

Building 1:15

bump 266:19
305:1

bunch 225:16

burden 41:15,16
42:12 43:8 59:22
90:13,16 91:9
121:2,3,19 219:6
220:2,14 221:2
222:10,12 223:4
224:3
229:10,15,16,21
232:1,15 236:20
242:12 243:16
246:1 247:1
282:6,8,9,11
310:14,20 311:9

burdened 42:13

burdens 90:14

burdensome 42:10
284:14

Burkholderia 247:15

burns 226:14

Bush 117:17

business 240:14

busy 140:4,11 239:20

button 329:22 330:3

buttons 35:19 329:17,18

buy 319:17

_____
C
_____

C-16 278:5

C-49 111:19 124:17

Cahill 233:1,2 234:19

calculate 50:2

calculating 181:13 328:8

calculation 325:3 326:19 327:3

California 215:2,12

Campus 1:15

Canada 138:6 157:6 159:15

cap 35:16 148:2

capacity 48:5 60:7 64:12 67:8

Capital 1:20

capricious 152:6

capsule 35:17,19 68:19

capsules 27:9 35:12 36:3 45:20 47:11 94:13 95:6

155:3 245:15 246:2,3 312:11,12,13

capture 204:2 208:18 314:12

captured 316:7

captures 216:14

capturing 313:16 329:4

care 3:10 4:14 5:13 7:15 14:14 19:15 20:5,11 21:13 22:9 27:20 47:18 50:20 51:7 63:10 67:14 79:22 84:10 91:22 92:8 150:10 161:16 215:20 220:2,14 221:2 222:12 224:4 227:22 229:20,22 230:11 231:3 235:5 241:22 243:2 258:15 271:11 277:16 307:1,2,9,19 308:11 310:18 311:1,10 336:10

cared 296:1

career 233:7 258:16

careful 79:2 248:18 261:12 262:14 304:13 339:12

carefully 141:18 186:10 213:22 340:18

cares 224:13

Carolina 8:9,10 14:15 20:22

carried 53:22

57:10,21 126:21 127:2 128:7,11 171:4 185:7 189:20 190:9 278:15,21 279:2

Carroll 214:14

carry 57:6 167:22 190:20 260:7

carrying 247:14

carve 323:14

cascade 39:1 40:2,4,12

case 46:14 52:4 97:5 123:15 135:12 176:6 181:3 183:18 190:17 194:20 195:9 258:21 259:22 261:4 271:9 274:12 281:22 285:8 286:14 297:1 310:7 312:15 318:6

cases 37:16 71:4 89:11 181:20 203:3 205:6 314:6 318:4,12

cast 303:13

Castile 6:5 19:3 93:2 100:4,5,18,22 101:6 102:3,9 105:17 116:18,19 121:15 278:16,17 280:19 282:17,18 335:19,20 337:11 338:8 344:22 345:1

Castile's 143:21

Cataletto 6:13 18:22 336:5,6 337:4,5,8 345:10,11

catalogued 313:13

cataloguing 131:12

categorically 291:20

categories 197:2 200:14 230:17

categorize 211:12

category 197:4 226:5 239:14 253:17 254:16 317:2

Caucasian 161:15

cause 39:12 60:14 137:20 204:19 248:2 273:3 300:12

caused 28:5 94:19 97:11 118:1 244:14

causes 39:1,2,7 71:2 82:4

causing 154:18 157:9 216:20 222:9 302:20 312:6

caution 146:16 305:7 310:12,14,21

cautious 90:15

caveat 267:14

caveats 146:14

CDER 1:2 2:7 10:10,14,18 11:9,13 12:15 15:9,17 16:11

celebrated 215:1

cell 18:5

cells 34:19 241:3

center 1:2,14 20:1
46:8 82:8 104:16
120:14 131:21
152:14
239:10,13 245:6
276:5,22 277:14
308:13,18,21
310:17 311:1
329:7 335:13

centers 46:6 63:8
79:18 132:21
138:6,8,11 139:7
143:17 229:22
273:2,4 276:19
279:21 304:9
306:17
308:11,15
329:2,6 336:9

cepacia 247:15

certain 30:18
88:18 110:19
130:16 163:18
264:12 267:2
268:3,13,14
290:9 307:14

certainly 108:6
109:16 110:14
111:14
112:10,11
140:12 141:15
143:14 149:6
241:15 258:16
262:7 279:17
285:14 293:1
296:18 301:7
302:12 311:14
320:15 322:1
323:4 327:9,16
331:17

certainty 58:3
231:21

CERTIFICATE

347:1 348:1

certified 79:18

certify 347:3 348:2

CF 28:14 36:19
39:20 40:9
41:6,15 48:1
50:9,16 59:21
60:4,14,20 61:19
62:22 63:7 65:8
66:1 67:1,4,22
69:22 79:6,17,18
80:15 81:8,21
82:2 84:7,10,12
85:2,5,9,12,22
86:9 87:12,17
88:7,9,11
89:10,19 90:4,12
91:14 92:1,17
98:12 105:4
106:22 120:13
132:12
144:12,13
149:14 150:6
152:13,17
153:16,18,21
154:3,12 155:6
157:6 159:1
189:8 190:11
194:17 197:14
214:17 215:1,3
216:17,19
217:18
218:4,12,21
219:4,5,19 224:4
228:14
229:6,19,20
232:15,19
234:1,6,9,13,14,
17 235:11,19
239:2 240:8
242:12 243:12
244:13,17 245:5
248:2 255:10
258:7,15
264:18,21
265:1,3,5,8,12

267:10
276:5,19,22
277:14,18 278:6
281:3 282:2
286:11 292:15
295:13 303:5
304:9 308:11
310:17 311:1
312:21 313:14
315:8 317:13
328:19,21 329:3
331:19 334:15
335:12 336:9

CF-202 45:14

CF-301 44:15 45:6
47:20 50:15

CF-302 44:18 64:3
83:18 220:10

CFers 217:7

CFF 151:1,5

CFR 252:21
254:18

CF-related 69:8
244:15

CFRI 214:16
217:5

CFTR 28:7 37:12
39:1,2 40:4,6
238:5

chair 18:11 20:16
22:6 214:3 256:4
257:20

Chairperson 3:7
12:4

challenge 42:8
100:12 104:19
108:22 112:20
122:20 123:22
126:14 157:10
262:1,21 322:12
335:14

challenged 56:21

challenges 41:17
60:14 217:7

challenging 44:8
60:18 67:11
284:22 285:4

chamber 35:18

chance 110:10
137:8,14,21
194:3 218:22
237:13 244:5
250:15 291:7,21

change 29:5,16
45:15 47:21
48:15 51:1,12
53:8 65:5 69:16
102:13,14 136:3
141:21 142:2,9
147:5 148:20
149:11
158:9,12,14
159:18 164:20
168:9 171:16
173:13,22
178:21 190:14
191:16 192:13
194:15 195:5,13
206:15
208:21,22
211:12,14,19,20
214:8 219:22
249:6 250:9,21
259:10 295:14
307:6 322:4
326:22 330:2

changed 61:20
112:22 241:1,3
246:2 317:12

changes 51:10
60:9 83:10,18
105:2 111:20
119:12,13 143:9
147:11,12
156:2,9 191:8,15
192:4 209:4
326:16

changing 68:8 137:5 246:9

channel 266:17

Chapel 8:9,10 21:1

characteristics 122:19 161:11

characterization 172:13

characterized 67:21

charge 16:20 134:16 207:8 251:14,16,18

charged 256:3

Charles 9:19 21:2

Charlton 14:7 36:14 67:17,18,19 94:21 95:4,15 97:7,11,22 98:3,5,18,21 99:1,9 100:16,20 101:2,11 104:1 113:1,7,9,10 114:13 299:2 303:16 308:2,3 318:4,10,17,20 319:1,5

charts 313:19

check 105:1 122:13

Checking 106:14

chemotherapy 182:19

chest 143:20 154:4 198:15 218:13 219:8 244:21

Chicago 2:21

chief 13:20 20:4 43:17 240:3

child 42:15 229:15 237:21 293:9,13

children 13:16 24:4 31:21 38:12,13 67:1,22 89:1,6,19 108:10 135:11 136:6,11 139:9 140:20 141:2 143:9 144:9,11,12,22 145:3 147:17,22 150:4,5,6 216:3 250:14 256:17 260:3 262:12 263:17 267:13,15,17 273:14 275:7 276:19 291:5,22 293:3,14 296:4 299:12,19,22 300:20 303:9 304:12 305:16,17 310:5 312:16 315:20 319:9,20 320:12,19 321:5,22 322:5,8,13 332:3 333:16,20 334:21 335:7 337:14 338:4 339:6,11 340:21 344:14,20

Children's 2:14 6:7 8:19 19:4,8 20:2 235:4

choice 45:17 91:5 155:22

choices 91:4 239:9

choir 247:9

cholistin 222:11

choose 32:20 213:11 304:13

choosing 342:20

chose 142:22

chosen 155:15 191:6,8

Chowdhury 10:5 21:15 268:19 269:16,18

Christ 240:12

chronic 39:8,11 59:21 85:3 91:14 112:18 155:19 190:15 194:20 199:2 202:16 206:10 305:14,15

chronically 115:15 162:3 194:13 196:11

chunk 228:4 314:7

church 247:9

ciliary 34:18 216:15

ciliated 34:18

Cindy 2:4 12:7 20:7

circumstances 335:16

cite 41:18

cited 125:12 229:17

cities 311:5

claims 59:17 138:13,15

clarification 100:6 106:19

clarifications 145:13 151:14

clarify 100:9 101:13 299:2,13

clarifying 14:17 16:16 93:3 197:6

207:21 208:3

clarity 294:4,5,8,15 296:8 345:2

class 197:12 231:14 237:10,13 259:8 260:21 270:19 335:2 339:11

classed 58:15 101:17

classic 258:22

classified 173:7 174:3 200:8

classify 172:18

clean 232:6

cleaning 36:5 42:2,4

clear 98:15 156:14 167:5 216:16,22 217:8,11 218:15 230:20 233:18 234:5 238:6 283:3 284:6 291:20 294:18 296:14 302:15 307:22 324:2,10 326:18 342:6

clearance 27:18,22 34:14,21 35:6 39:5,7,18 40:8,12,17,19 41:3 42:17,18 43:22 60:11 61:16 64:13 65:22 82:17 88:19 92:2 120:11 154:2 190:14 217:16,17 219:13,15 225:10,13,17 226:16 228:3,19

235:8 238:10
259:6 285:3
323:21,22

cleared 223:21

clearer 102:8

clearing 120:10
244:20 304:1

clearly 106:1,7
141:8 142:20
220:20 259:13
285:13
303:2,8,20,21
322:12 340:22

clears 302:14

clinic 2:14 20:2
111:11 113:12
235:20 236:12
303:5 319:11
323:10

clinical 4:7 5:8
6:17 9:6
10:13,17 14:11
15:6,8 16:13
18:18 19:1,2
21:9 26:20 28:21
30:19 31:2,12
33:16 34:14,20
36:16,21 44:1,3
54:4 63:19
69:2,4 71:19
77:10 78:8 79:4
81:13,20,21 84:4
87:20 90:4
100:11 103:7
104:12
105:8,17,21
106:13
108:19,21
110:17 111:14
117:14 118:19
120:13 131:5
132:17 139:21
140:12 152:19
153:4,7,10,11
175:7

188:10,15,18
193:17 196:2
226:8
230:6,7,8,11
232:9,17,18
236:19 245:7
253:21 264:4
279:5 283:22
284:13 286:8
290:13 292:7
295:10,11,15
298:13 299:21
321:9,10 326:15
327:16 329:9
336:2,8

clinically 30:20
44:2 48:4 54:14
60:21 76:4 83:15
85:12 92:6
105:21 117:13
122:16 191:5,18
193:11 195:7,14
206:4,16 207:7
209:4 221:21
252:9 253:15
254:2,12 272:8
327:12,18,20
328:12

clinician 81:18
88:5 102:15
224:17 285:10
293:20 315:13

**clinician/
researcher**
239:2

clinicians 41:8
43:13 81:8 88:11
116:21 134:1
139:14 144:3
232:9 343:13

clinics 277:19

clogs 244:20

close 170:17
272:10 295:2

closed 330:3

closely 27:11
199:9 249:7
250:17 323:12

closer 99:6 147:12
150:17 211:1

closing 35:18
207:8

club 222:21

cluster 135:10

co 156:5

Coalition 20:16

coarse 146:13

coast 215:2,12

co-chairs 81:22

Code 252:21
270:14

coded 197:14

cohorts 231:5,7

coincide 306:17

collapsing 140:15

colleague 277:11
310:18

colleagues 106:14
140:14 229:20
308:9 345:12

collect 80:2 150:16

collected 48:6 52:8
151:4 305:11

collecting 151:2

college 6:9 219:20
221:12

colonization 39:10

colonize 216:20

color 214:8

Colorado 9:14,15
19:12

Columbus 6:11

19:5

column 56:11
59:14

combat 236:6

combination 45:5
117:22
118:13,15
133:15 144:2
219:14 341:10

combined 76:9
160:18 196:13
204:2

comes 122:2 237:4
284:4

comfortable 83:21
105:13 193:11
252:15 304:18
338:3

coming 61:14
129:1 143:16
152:12 286:4
346:4,6

comment 103:7,8
110:16 111:3
113:2 118:19
120:5 140:1
148:12 150:2,21
156:12 163:19
180:8 267:4
278:17 280:6
296:6,8 306:22
308:2 313:9
316:2,10
319:14,17 321:9
324:4 327:21

comments 114:20
213:16
248:16,20
258:17 283:22
324:5 332:8
339:17 341:11

committed 80:9

committee 1:5

2:5,9 3:3 4:3 5:3
12:3 16:20
18:2,12,14 20:9
22:8,9,16,22
23:1,3,13
24:1,19 25:1,20
26:11 28:3
32:7,12,18 33:7
82:1 91:15,16
93:1 132:12
151:9,21 152:16
196:3 205:15
207:9,12,19,20
212:8
213:1,9,14,17
229:4,9 231:18
232:12 234:22
248:17,19
251:14,16,18
252:18 255:21
256:2 258:1
260:22 297:7
325:12 328:20
345:19 346:8

committees 23:8

common 37:13
49:11
50:11,12,14 63:2
69:10,19 70:18
71:7 74:4
87:12,13,14,16
88:8 98:13
109:13 131:8
153:22 167:19
189:1 197:17
201:4 204:21
216:7 315:20
325:19

commonly 27:2,19
85:11 90:4
131:10 153:20
204:18 296:16
323:9

community 152:18
154:12 214:19
217:4,14 239:3

240:4 241:7,16

company 1:20
25:10 233:3
269:9 270:6,22
279:15 282:22
326:3

comparable 50:9
52:20 65:16
76:17 77:11 78:9
85:21 160:8
226:22

comparative 239:3

comparator
290:12

compare 52:22
122:17 134:10
138:22 183:10
194:10 316:8
317:10

compared 29:17
44:22 45:4 51:4
52:12 53:7 61:8
64:16 66:3 73:13
74:19 83:14 85:9
104:3 114:15
115:12 127:6
133:14 136:18
174:6,13 178:7
179:18 180:3
183:9 194:12
200:14 210:20
307:2 309:5,6
320:12

comparing 45:2
84:8 116:9 159:5
181:15

comparison 116:3
117:8 173:20
175:10
194:14,19
206:10 290:5
325:18

Compassionate
244:12

246:11,13

compelling 90:7

compensated
36:22 81:17
129:6

competitors 213:4

compiled 298:17

complete 90:20
101:18 160:22
167:13 183:8
185:5 199:13
206:20 334:8
348:7

completed 59:15
86:6 91:15
157:21 169:13
178:17,19 330:4

completely 129:21
137:11 166:22

completer 90:6

completers 50:7
59:18

completing 102:2

completion 78:12
167:14

complex 154:3
222:8 301:14

compliance
23:8,13 36:21
137:5

complicated 237:5

complication
88:10 132:14
133:22 134:9
194:8

complications
28:19 234:2
244:15

comply 42:10

component 75:14

342:2

compound 301:7

compounded
287:14

comprehensive
80:14

comprised 44:21
47:7 49:6 62:9

compromised
216:4

concentrated
339:1

concept 322:12

concern 81:10
83:20 87:9 88:5
106:8 121:18
163:5 170:6
178:12 186:13
244:18 291:1,2
298:14 304:17
344:19

concerned 96:12
102:16 130:20
288:6 291:8
294:8 340:11

concerning 25:3
196:2 202:21

concerns 31:16
105:18 129:11
189:2 199:5
261:16,20
262:5,7
275:10,22
276:18 291:16
329:10
340:7,16,21

concise 258:9

concisely 207:19

conclude 44:14
189:4

concludes 207:15

248:14

conclusion 22:15
53:13 171:18
175:1 178:5
179:9 193:3
224:1 231:19
325:13

conclusions
117:20

conclusiveness
294:8

concomitant 85:15
86:2 137:6

concur 280:19
320:15

concurrently
29:19 164:8

condition 71:3,6
197:15 311:8

conditions 59:21
253:6 254:21
255:1,3 266:1
267:6,18 268:1
269:5,10

conduct 285:1

conducted 29:19
46:4 53:15 94:7
157:5 159:3
164:7 165:17
189:19 213:21

conducting 284:12

Conference 1:14

confidence
66:11,20
168:13,19
189:22 192:6
194:7 271:12

confident 108:16
185:21 187:19
208:18 344:8

confirm 45:19

confirmatory
93:21 156:16

confirmed 46:11

conflict 12:6 22:19
23:5,9,14,20
24:20 179:13
220:12

conflicts 23:18
24:2 229:4

confounding
46:18 252:7

confusing 123:10

congested 216:12
246:19

Congress 23:15

connection 24:21
213:6

Connett 7:5 19:16
278:2,3
333:21,22
338:20,21
343:18,19

consensus 132:19
285:5 315:11

consent 50:12 63:3
329:7 335:17

consequences 39:2

Consequently
76:6

conservative 57:16
63:21 64:9
128:12 142:18
170:16 171:11
312:16

conservatively
57:21

consider 41:15
51:19 66:19 74:3
76:1 81:8 88:14
93:12 125:5
186:15 210:11

224:16 228:10
263:1 296:20
297:7 315:15
335:10 345:17

considerable
81:19

consideration 31:8
44:12 140:2
199:19 213:17
228:22 248:18
257:11 270:21
271:7 277:5
288:1 296:18

considerations
42:1 266:22
322:9

considered 37:15
45:20 54:13
75:22 78:3,4
156:15 172:12
282:1 287:7
327:12

considering 167:5
172:6 205:16
256:20 269:1,5
284:20 330:17

considers 232:13

consist 154:3

consisted 62:15
156:21

consistent 35:9
43:21 60:9 61:11
64:6,13 65:6,21
67:6 81:3 85:11
138:10 172:2
174:10 179:4
190:3 308:14
329:6

consistently
207:1,2

consisting 253:2

consists 155:2

consternation
294:21

constriction 27:16

constructed
186:22

construction
216:11

consultant 2:5
25:11 37:4

Consultants 3:15

consulting 24:7
32:13

consumer 3:14
310:15

consumers 311:9

consuming 220:21

cont 14:4

contact 18:9
315:12

contacts 188:18

contained 49:19

containing 35:12

contains 82:19

contaminated 42:6

contents 12:1 13:1
14:1 15:1 16:1
17:1 155:2

context 32:9
105:14
190:12,19
193:18 195:22
212:19 255:9,10
268:11

continue 43:12
60:1 79:12,15
86:8 87:4 117:2
120:22 122:4
163:17 172:15
201:1 240:6
248:8 260:15

329:19 330:13 340:4

continued 3:2 4:2 5:2 6:2 7:2 8:2 9:2 10:2 11:2 13:2 14:2 15:2 16:2 17:2 63:19 167:9 179:3 182:7 200:21 201:1 204:15 249:17 257:22 309:9,21 310:6 335:17

continues 103:14 190:7 203:10 215:16 216:2 244:17

continuing 165:18 199:2 310:9

continuous 58:7,19 172:10 178:21

contracts 24:7

contradict 188:4

contraindications 267:22 268:14

contrast 231:14

contribute 38:17 52:17 329:2

contributed 63:8

contributes 182:11

contributing 39:16 138:17

control 29:8 30:5 43:10 45:9,22 47:10 49:20,21,22 50:6,7,13 51:4 52:13 53:4,8 57:2,6 61:8,18 62:15,16,21 64:16 66:4 68:8

69:17 70:2,4,14,21,22 71:16,17 72:21 73:14,17,21 74:18,20 75:7 76:11,14 77:1,6,11 78:10 83:14,19 107:2 114:16 115:12 116:10 127:6,7 130:22 133:5 134:3 135:9,20 136:2,12,13,21 137:2,10 139:5,6 142:7,13,14 146:9 149:9 158:20 159:6,10,14,16 160:3 164:6 166:3,15,17 167:11,12 168:15 171:16,19 173:1,14,21 174:7,8,13,17,19 177:14,19 178:16,19 179:5 183:11,12 187:8 188:8 192:17,21 193:20 194:13,16 197:16,20 198:3,8,11,20 199:18 200:16,22 201:7 202:14 203:6,8 204:6,14,21 205:2,4,7,11 206:10 210:16,21 266:15 274:7 290:6,12 295:9,12,15 297:16 298:6,20 307:8 308:15,19 309:14 311:22 312:3,6 322:1

332:18

controlled 29:13 46:8 68:14 157:12 159:4,22 253:2,13

controls 200:15 202:2,5 207:2

conundrum 311:22

convenience 36:6 232:1

convenient 41:4 120:17 223:9 248:5

convening 22:21

conversation 121:8 185:11

conversations 22:10

conversely 249:19 282:5

convince 186:18

convinced 186:17

convincing 120:8 207:5

cooperation 214:4

COPD 255:20

coral-like 303:13

core 131:13 133:8 135:3 324:15

cornerstone 92:1

correct 79:13,21 94:15,16 101:11 109:21 130:9 144:20 210:6 211:2 348:6

correlate 119:13

correlation 119:15 121:10 285:9

corresponding

172:20 330:3

corresponds 173:5 330:1

costs 231:3

couch 242:20

cough 70:5 71:3 72:3 73:12,15,17,19,22 101:19 109:12,14,16,19 110:4,10 111:9 112:13 164:12 198:14 201:9 204:17 216:12,16 217:7 227:16 228:13 245:10,15,16 246:20 285:5,6 302:20,21

coughed 303:6

coughing 82:20 169:19 247:10 303:13,14

Council 54:3

counsel 347:8,11

counselor 244:7

count 151:4 317:16

countries 272:18 273:1

country 164:4 217:6 272:12,22 277:20 306:19 307:17

couple 114:20 126:11 130:15 143:12 259:3 287:13 306:8 314:22 332:16

course 65:11 105:14 146:22 148:1 153:1

157:17 183:8
187:14 231:16
250:5 266:9
284:8 293:21
308:20 310:4
321:15

Court 348:3,5

courtesy 214:1

cover 126:12
250:1,11 300:4

covered 23:9

crackling 245:18

create 116:2 206:9
305:15

creates 194:9
259:14

creating 306:6,7

CREDAs 24:8

Creighton 9:7
20:19

crises 215:22

criteria 48:7 61:5
72:13 114:7
160:7,8,13
269:14 314:11

criterias 269:22

critical 3:10 4:14
7:15 14:13 19:15
20:5,11 21:13
64:2 91:22 154:2
231:10

criticism 171:9

criticized 184:21

cross 57:18

crossed 192:7

crossover 29:3
45:1,2

cross-sectionally
57:8

crucial 180:15

cultures 314:21

cumulative 163:15
177:6,8 180:1
192:7 250:4,6
288:22 289:8
312:6 332:19

cup 82:20

cure 153:16
233:10,22
234:13,16

current 28:18
39:21 41:2 42:15
79:6 147:20
236:7 239:5
241:14

currently 34:2,5
40:18 85:1 233:6
243:4 244:11
287:11

curve 173:3,19
187:2,4

curves 186:19
188:1 193:1

cut 152:4 222:13
234:9 247:4
249:2

cute 218:10

cutoff 103:4
192:16 319:8

cutting 152:5

cycle 39:13 82:3
83:2 91:3
219:11,20

cystic 21:3 24:14
26:15 27:7,18,20
28:2,5,8,13,18,2
2 33:6,9 34:3,22
35:5 36:10
37:7,10,13
38:2,4,8,9,12,15,
22 39:19 40:1,20

42:8,17 43:19
44:20 46:11 68:4
69:10 72:2 74:4
75:5 80:10,13
81:19 82:16 90:5
97:10 106:5
131:7 153:12
154:21 163:1
176:14 190:19
214:15 215:14
216:1,4 217:4
218:7 220:14
224:12,13,21
225:9 229:8
230:13 231:1,10
233:5,7 234:2,12
235:3 238:3
240:4,5,14,21,22
243:3,8 244:8,14
247:17,21 248:9
251:4 254:7
256:11
257:2,7,15
264:12 265:6
269:3,19 279:20
282:20 284:11
289:15 292:16
295:22 296:1
301:16 329:1
330:20 336:14
341:7

_____
D
_____

daily 27:10 29:7
45:1,3 47:11,17
155:2 157:16,19
196:8 243:2
244:10 256:10
257:1,15 258:5
330:19 341:6

damage 39:12
238:14

Dance 242:19

dark 303:12

data 26:13 30:3

31:9,19 33:15
43:18,21 44:5,7
46:18 51:13
52:2,3,8,17
53:9,18
54:4,8,9,18,20
55:1,2,8 56:9
57:8,13 58:22
59:6 60:6
65:7,17 66:5,14
67:3,17
68:4,5,14 69:1,2
76:19 80:12,20
82:7 86:13 95:19
96:4,9 98:1,3,6
99:13 100:14,16
108:17 109:9
112:8 113:8,11
117:16,21
118:6,8
119:2,5,11
120:6,8,12 121:6
122:17,20,22
124:9,10
125:3,19,20
126:3 127:3,12
131:15,21 133:7
134:21
135:10,19,20,22
137:12
138:2,4,9,13,14
140:21
141:1,4,13
142:9,16 143:14
144:18,20
145:2,6,15,16,18
,20 146:7,15,18
147:2,8
148:9,11,15
150:16,19
151:2,4 152:21
153:8 155:18
158:2 162:14
163:16 165:1
166:17,18
168:2,4
169:2,6,13,15,20

170:1,10,19,21
171:6,13 172:6,7
173:7 174:3
175:18,19
176:2,6 178:12
180:17 184:4
186:3
188:16,19,20
189:11 190:6,10
192:5 194:22
195:17,20
201:14 204:1,7
205:19,22
206:5,9 207:5,13
225:18 226:1
229:18
230:15,16 231:4
248:19 249:1
250:3 252:7,14
256:21
257:9,13,19
272:14
273:7,12,19,20
274:2 276:4
277:2,21 278:3
279:6,7,11,13
280:9,11,15
287:2
288:10,15,16,18,
22 290:3 292:14
293:4 294:4,9
295:7 298:18
299:10,20
300:17 305:11
306:10,16,19
307:5,15 308:18
310:10 312:17
313:1,6
317:2,17,19
320:10
321:3,6,13,15,16
,19 322:4,7
323:13 324:12
325:11,13
326:1,8 329:8
330:17,21
332:19

333:3,16,19
334:3,13 335:21
336:3,9,15
337:12
338:2,10,22
339:5 341:4,8
342:5,7,18
343:11,21
345:3,8

database 80:14
151:1,5 199:7
202:8 207:14
250:15

date 71:20 241:10
264:1 348:12

daughter 241:12
242:19

David 3:6 12:4
18:11 20:4 333:8
339:13 343:6

day 30:12 31:5
33:22 41:19,20
74:21 90:18 91:4
102:18 103:15
107:15,16
108:4,7 116:9
128:21 129:5,20
130:1,3,7,10,13
140:4 155:3
158:5 215:19
218:15
219:7,9,10
220:18 221:8
222:13 228:4
229:14 232:16
235:11 236:4,16
237:21 242:16
243:10
244:19,21
245:22
246:3,4,19
247:5,12 248:1
277:13

days 107:18
140:11 147:21

191:11 218:7
238:18 242:22
243:4,12 244:13
246:15

day-to-day 230:10

DB-II 11:7,13
15:14 16:8

deal 132:13
229:14,16
265:10

dealing 251:4
296:3

dealt 262:9

Dean 4:6

death 39:16

deaths 38:7 196:15

debate 323:6

debilitating 37:9

decade 152:12

decades 241:9

December 156:7

decide 117:1 121:3
136:17 255:13
321:6

decided 208:8
246:10

deciding 284:19

decision 59:8
67:11 108:7
207:21 236:13
262:21 263:4
267:1 270:11
288:20 293:22
313:7

decision-making
32:6 212:17

decisions 79:4
152:5 236:1,16
262:14 263:6

declare 264:2

decline 38:16,18
43:2,4 48:2
82:5,14 145:9
216:20 217:2,12
247:16

declined 86:13
124:20 246:19

declines 38:10
60:15 101:8
124:15 127:22

decrease 272:16

decreased 231:2
314:18 324:21

decreases 35:2
58:21 225:20

decreasing 236:19

dedicated 37:7
88:10 214:17

deep 35:21 245:17

default 101:5

defect 183:17
184:1 238:2

defense 39:6

define 31:8 58:10
281:13 290:10

defined 165:14
200:2 201:17
206:12 256:22
259:10

defining 280:21

definitely 225:19

definition 49:18
61:1 62:7 127:10
158:1 261:1
281:15 297:10
319:16 335:1

definitive
280:14,15

definitively 304:8

degradation 39:14

degree 30:3 52:18 193:10 308:19

degrees 305:21

dehydration 39:3

delay 38:16

deliberate 26:21 30:1

deliberations 274:19

delineated 208:14

deliver 188:12 236:9

delivered 207:9 219:18 221:14 232:4

delivery 35:11 72:1 237:7

Delphi 132:20

delta 139:8 144:19

demarcation 192:15

demographics 50:15 68:2

demonstrate 36:11 252:22

demonstrated 30:13 51:3 82:7 85:22 158:14 179:11 192:21 237:15 253:1 323:22 335:15

demonstrates 106:1 158:10 193:7 196:12 197:8 254:1

demonstrating 168:13 222:21 253:13 326:21

Dentistry 5:10

Department 2:18

7:14 8:7,16

dependency 301:12,17,21

depending 155:14 236:14,15

depends 187:2

depletion 39:2

deposition 35:8 300:3,10,19,20 301:13,18,21

derived 43:21 230:16

describe 36:12 45:7 162:12 163:6,9 186:10 208:9 222:3 303:13

described 153:15 156:20,22 165:7 169:3 181:8

describes 80:20

describing 181:12 264:4

description 44:4 94:5 163:4,21 166:7 170:15

descriptive 62:3 177:5

deserve 231:20 261:17,18

design 29:12 45:1 46:7 158:3 159:19 163:5 164:1 220:15 253:20 280:13 283:22 327:2

designated 2:2 12:7 20:8 46:5

designed 36:6 51:8 58:6 164:8 286:17

320:14,21

designing 283:8

designs 44:4

desirable 53:16 172:10 284:8

desire 40:3 261:13,14 263:3

desired 43:12

desires 262:20

desperate 262:16

desperation 262:17 263:4,11

despite 28:13 37:18 44:15,17 54:14 63:17 101:8 103:11 236:11 245:3 247:14 296:21

detail 45:7 51:21 70:16 156:20 162:13

detailed 26:17 44:4,13 80:3

details 22:14 101:1 231:17

detect 58:20 60:19,21 327:4

detected 259:19

determination 31:6 115:19 255:9 257:12

determine 76:2 194:11,21 255:5 299:21 313:20 326:7

determined 23:12,18

determining 252:20

Detroit 218:3

develop 114:7 270:22

developed 218:17 265:4

developing 150:13

development 112:19 155:10 156:19 157:2,4 190:12 271:2

developments 225:16

device 155:4 219:17 221:14 302:1,5

devices 18:6

devoted 230:3

devotes 215:19

DFO 330:9

diabetes 244:15

diagnosed 37:17 218:8 244:13

diagnosis 46:11 93:21 105:21 106:20,21

diameter 35:10

Diana 104:15

dichotomies 186:14,15

dichotomized 58:22

dichotomous 58:12 59:5

dictated 48:20

dictates 243:4

dietary 68:21

differ 155:14

differed 165:11

difference 58:20 59:4 60:19 63:13

64:16 66:22
69:16 89:5
118:11 133:20
139:2 142:4,6
160:9
168:9,11,16,19,2
1 171:15,20
172:1 173:18
174:5 175:22
176:11,16,22
177:12,17
178:1,2,3,9
179:11,17,20,22
180:4 187:10
192:18
203:11,20
210:5,14,19
250:20 273:14
281:12 297:17
299:13 308:12
309:19 320:11
321:1 327:4
328:13

differences 66:3
71:12 83:15
118:15 174:14
295:8

different 54:17
85:16 93:22 95:2
111:13,15 112:4
116:3 120:9
123:6 135:6,15
144:11,13,14,16
145:1 148:16,17
149:4,5 164:17
178:5 181:3,18
184:16 193:3
194:9 204:10
208:15 212:2
231:5 259:3
285:22 293:10
300:7 301:6
307:9 308:20,21
317:4 322:13
323:3,14 335:5

differential

30:4,11 31:9
52:13 53:18
115:10,20 116:2
124:4 127:5
163:7 166:8
167:9,17
175:14,18 176:5
177:4 179:1
193:19 194:9
205:19 274:7
299:8,19
300:9,19 326:9

differentially
168:2 169:2

different-looking
187:22

differently 210:9

difficult 106:22
108:22 169:7
187:16 206:6
221:13 237:5
284:3 301:4
307:15

difficulties 117:19

difficulty 106:5
239:7 284:11

digestive 218:12

dignity 214:1

dilator 47:1

dilemma 279:16
280:2

diminishing 84:22

direct 72:7 110:6
213:3 300:12
336:2

direction 187:20
263:2 273:3
321:20 324:10
347:6

directly 39:3 40:4
79:22 81:9 142:1
150:16 169:21

238:2 302:4

director 3:15 4:7
10:6 11:6 14:8
16:8 20:17
21:7,16 67:19
104:16 214:15
229:6 235:3

directors 279:21

disability 233:6

disagree 134:6
277:11

disappear 127:15

disclose 25:2,5
37:4 81:15 91:17
129:6 214:20,21
218:5

discomfort 198:15

discontinuation
70:19 71:2,5,6
73:19 79:5 115:4
163:8,12 166:8
167:9,15,17,20
169:16 170:4,22
175:14 177:4
197:4 198:19
202:13 204:20

discontinuations
178:14 198:4,12
201:22 205:1
275:16

discontinue 117:2
123:14 145:16
182:11 184:3
259:15

discontinued
70:22 107:12
172:11 173:6
196:22 197:1
198:11

discount 132:5

discreet 91:12

discrepancies

164:22

discuss 36:9,14,15
61:19 80:17
105:11 115:17
150:22 154:7
156:17 162:16
163:2 193:13,15
205:13,16
207:10
256:3,8,14,15
258:3,10 261:11
311:14 319:18
322:17

discussed 21:20
24:18 31:15
70:16 128:18
133:9 141:7
146:20 160:16
174:21 191:19
201:3 330:15
331:1 336:16

discussing
22:14,17 115:14
188:15 221:5
316:13

discussion 22:2
24:10 26:12
31:4,6 149:12
151:20 154:9
155:12 189:5
195:18 199:4
202:19 208:1,12
223:18 248:21
251:9,19,21
252:2,12
256:2,7,13,18
257:22
258:1,3,12 269:1
290:18,19
310:13,16
319:19

discussions 23:21
25:13 80:10,18
161:10 196:4
208:6 252:13

disease 28:14,20
29:1 37:9,11,15
38:4,9,19,20,22
40:2,12,14 41:8
43:11 44:9 46:5
67:10,15 69:8
74:13 75:10 81:3
82:3,16 84:12
85:2,12 88:9
89:7,9 92:17
112:11 131:9
144:22 148:5
153:13,19
161:13 196:9
201:13,17
202:2,4 205:9
217:2 222:9
233:10,15 234:1
236:6 240:22
245:4 246:8
247:20 254:7
255:11 260:21
264:5 271:6,8
293:9,12,13
305:20,22 341:1

diseased 215:10

diseases 4:9 8:18
19:21 37:14
255:17,18
264:12 270:20

disinfect 232:6

disinfection
236:10

disorder 28:5

disparity 203:11

displayed 198:18
330:5

displays 172:17

disposable 36:5

disproportionate
170:4 306:15

disproportionatel
y 198:17

distinct 198:16

distinction 103:17
232:16

distinctly 212:2

distinguished
166:2

distributed 96:19
178:8

distribution 79:17
94:18 95:19 96:4
147:21 186:11
300:5

distributions 95:2

diuretic 27:3

diverse 68:1

divide 320:3

division 2:5,19
3:10 4:14 5:9
6:14 7:7,15 8:18
10:7 11:7 12:11
15:14 16:8
20:13,19 21:7,16
152:10 163:6
165:6

divulge 229:5

DNase 28:1 39:21
118:12 120:8
144:2 154:6
283:4,9 301:19

doctor 246:10

doctors 331:19

document
211:18,20

domain 176:14

domase 41:20

done 18:7 96:15
102:20 118:3
180:22 181:12
235:20 246:4
263:5 266:16
274:10 286:16

289:18 301:7,22
316:4,5,16,20
325:2,10

dosage 68:20

dosages 343:1

dose 27:8
29:2,7,8,9
34:1,8,11 35:13
44:1
45:2,10,14,18,20
,21,22 47:8
49:13
93:5,7,10,13,14,
17 94:8,14,18
95:12 98:7,8,12
100:13,19
122:11 133:13
137:10,18,19
155:1
157:4,10,16,22
158:11,13,14,15,
18,20 159:6,8,9
161:2 164:17
165:16 199:13
246:14 250:4
256:9,22 257:14
258:5 299:11,21
300:5,20,21
301:13
312:3,11,14
330:18 341:6
342:20,21

dose-response
158:7 342:19

doses 45:3,15
95:15 96:19
158:7 250:7

dosing 45:13 87:8
137:15 159:2
300:9 301:5,12

dotted 52:2 135:7
142:8,12

double 47:12 50:5
86:7 200:18

202:14

double-blind 46:8
47:22 51:5 62:20
68:7 146:3,9
164:1,6,21
197:10 198:21
200:12

double-blinded
29:13,14 159:4
193:22 196:14
198:6 199:16
200:20 201:7

double-lung
233:17,21

doubt 276:8
332:10

downplay 296:17

downward 82:11

DPARP
10:8,14,18 12:13
15:9

DPM 33:5,8,19
34:1,10 35:7
36:6,12,15,16,19
44:1 45:4,18
49:19,20,22
50:5,7,14 51:1
52:12 53:3,7
56:5 57:2,7,14
59:3,16,18,20
60:3 62:15,16,21
63:4,12 64:22
65:5 66:4,9
67:20
68:6,9,11,15,18,
21 69:1,15,17
70:2,4,13,15,20,
21 71:7,16,17
72:17,20
73:1,2,10,13,16,
20 74:18,19 75:7
76:11,14,21,22
77:6,11
78:9,12,16,21

79:7 80:19,20
83:9,12,21
85:10,15,21
86:1,7,9,10,21
88:1,6 89:3
90:2,10
92:4,10,13 107:2
110:20
113:12,17
114:1,14 118:13
124:8 127:6
130:22 133:4,14
135:8,20
136:2,10,16
153:1,4
154:10,21 155:6
157:4,16,19
158:1,11,13,16
159:6,9,13,16
160:3 161:2
163:1,4,19
164:5,12
166:14,15,17
167:11,12
168:14
171:1,15,19
172:21
173:11,21
174:6,8,11,16,18
175:5 176:4
177:13,18
178:3,6,16,18
179:5 189:6,8
191:3 192:16,19
193:4,15,20
194:11,13,20
195:11
196:1,5,7,8,18,2
0 197:2,16,18
198:2,8,12,22
199:2,5,8,13
200:14,18,19,20
201:6,9
202:1,3,11,14
204:5,14,20
205:3,9,14
206:10,11,13,18

207:1,3 238:15
256:16
297:15,16
298:4,19 307:7
325:8 330:18
332:1,2,3 336:12
341:5

DPM's 44:20 60:9
67:13 332:17

DPM-treated 71:8

Dr 18:3,17,22
19:3,6,10,13,16,
19,22
20:4,7,10,12,18,
21
21:7,9,12,15,18
22:20 25:5,8,10
26:1,2,8 32:1,3
33:2
36:8,10,14,15,18
37:2,3 43:15,16
60:4 67:16,18
81:13,15 84:1
90:7,13 92:19,20
93:1,2,3,4,7,9,10
,12,16
94:2,3,16,17,20,
21
95:4,14,15,20,22
96:3,4,6,7
97:3,4,6,7,11,20,
21
98:3,4,5,15,18,2
0,21,22
99:1,2,3,9
100:4,5,10,16,18
,20,22
101:2,6,11,12
102:3,7,9
103:5,7
104:1,13,15
105:17
106:4,18,21
107:5,6
108:13,19
109:2,11

110:11,14,16,18,
20
111:3,16,17,18
112:7,16,17
113:1,7,9,10
114:5,6,13,17,18
115:6 116:18,19
117:10 120:5,7
121:1,14,15
122:1,6,7,8,12,1
5
123:3,9,11,12,15
,19,20,21
124:13,14
126:7,9,10
127:8,9,10,14,15
,17,18,20,21
128:1,2,5,6,9,10,
20,21
129:5,18,20,22
130:1,2,3,6,7,8,1
0,12,13,14
131:1,3,6 133:6
134:6,8,18,20,21
135:2
139:12,13,20
140:1,3,18,19
141:4
143:4,5,7,8,11,1
8,19,21 145:11
146:6 147:15,19
148:6,7,12,14,20
,22
149:16,17,18,20,
22 150:1,2,21
151:7,12
152:8,15
153:5,12
162:17,20
174:21
180:7,8,12 183:6
184:8 185:10,11
186:13 188:12
202:18 207:9,17
208:3,5,12
209:20,21,22
210:9,22

211:3,9,10,16,22
212:4,12 214:12
217:22 220:5,7
224:7,9,10
229:1,3 232:21
234:19,21
239:22 244:2
248:11 249:2,3
251:8,15,17,20
256:4 257:21,22
258:2,10,11
261:6 262:7
263:19,20
264:17
265:17,18,20
267:3,5 268:19
269:2,12,16,17,1
8 270:13 271:17
272:5,6 273:8,9
274:14,16
276:1,3,17
277:9,10
278:2,3,5,16,17
280:18,19
281:16,19,20
282:17,18
283:20,21
285:17 287:9,19
288:9
289:4,6,13,22
290:1,17 291:19
292:20 293:1
295:5 296:5,6,14
297:4,5
299:2,7,8,16,18
300:3,4,11,14,15
,16,18,22
301:2,4,22
302:3,6,7,12,22
303:2,16
304:3,6,15,16
306:12,13,18,21
307:5
308:1,3,4,5,7,10,
13,17 309:20
310:4,11,18
311:13,20,21

312:8,19,20
313:8,10
315:21,22
316:1,9,10,11
317:6,13,21,22
318:4,8,10,15,17
,18,20,21
319:1,3,5,12,13,
18,22
320:1,7,8,9
321:8,11,12
322:15,16
323:1,6
325:20,21
326:17
327:7,21,22
328:14,17,18,20
329:14
331:2,3,5,6,7,11,
13,14,16
332:5,6,14,22
333:1,5,6,7,8,11,
17,18,21,22
334:10,11,16,17,
21 335:3,4,19,20
336:5,6,11,22
337:2,4,5,7,8,11,
21,22
338:6,7,8,14,15,
20,21
339:3,4,7,8,13,1
5,18,19
340:5,13,14,19,2
0
341:3,16,18,19,2
0,22
342:1,3,12,13
343:3,4,6,8,9,15,
16,18,19
344:4,5,10,11,17
,18,22
345:1,10,11,16
346:2,3

dramatic 173:3
228:17

drastically 246:2

drawn 119:6 187:6

draws 245:9

dried 258:4

drink 110:1 111:7

drive 43:2 90:21

driver 52:13
138:19 143:16
231:3 250:22

drop 82:19 84:2
102:1,11,17
103:11,13,14
123:13 173:3
185:17 231:9
250:10

droplets 216:11

dropout 30:4,11
31:9 122:10
124:5,19 125:1
166:12 193:19
194:9 205:19
206:9 259:17
274:7 290:3
326:9 340:8

dropouts 52:13
53:18 83:21
86:15 115:10,20
116:2 161:9
183:17 187:1,3
198:17

dropped 103:2
105:6 143:13
171:1 189:11
238:11 309:22
340:9

dropping 326:11

drops 82:9 101:15
105:10 124:1
184:7,15 230:18
250:6

drove 272:19

drowning 233:20

Druce 5:6

18:17,18 25:6,10
283:20,21
312:19,20

Druce's 25:8

drug 1:1,2 10:9
12:13 22:20
24:11 28:17 32:4
47:2,7,9 49:16
62:14 81:4 83:6
84:11 102:17
103:11
105:2,7,9,19
108:4 109:1
110:13 113:3
116:5 121:16
122:3 145:5,10
152:21 154:7
155:7,8 161:6
164:17 165:16
171:2 180:15
182:9 187:7,13
188:9 190:12
194:19 196:16
199:21 208:10
210:20 216:21
219:17,22
224:16 225:22
227:21 228:5,11
233:3
234:3,4,5,16
237:7,13 239:14
247:19 248:1,7
253:4
254:4,6,8,19,20,
22 255:2,5,13
259:3,5,7,8,13,1
5,21 260:15,21
262:1 265:7,11
266:17,19
267:20 268:2,9
269:2 270:19
272:3 275:3
278:9 279:10,15
286:15
287:11,15,16,17
290:11

299:11,14,21
300:8,12 301:5
302:13 303:3
304:1,4,5,10
305:18 311:18
312:3 322:9
332:12 335:2
337:17 339:10
344:3 345:13

drugs 1:4 2:9 3:3
4:3 5:3 10:10
12:15 18:12,13
20:9 22:22 26:11
110:22 121:12
144:6 153:18
218:17
219:3,6,7,14
231:14 234:5
239:4 247:22
255:16
265:3,9,13 271:1
301:8,16 325:19
346:8

drumming 215:18

dry 33:5 35:11,14
43:18 91:8 153:1
154:9 155:3
226:18 227:9
245:8
256:9,14,16,22
257:6,14 290:20
301:9 325:17
332:16

DSMB 165:17

due 41:7 49:12,17
52:14 70:19
71:1,6,18 78:5,7
90:4 101:19
102:1 124:5,14
159:20 176:10
188:22 190:6
191:11 194:2
197:1 198:4,9
201:22 204:17
205:1,21 206:22

233:6,15 319:15

Duluth 3:17

Dundore 13:8
33:2,3
300:4,16,18
301:2

Dundore's 278:5

duration 29:14
47:3 74:20 88:1
145:5
155:13,15,17
159:5

during 22:17
24:16 47:12
68:7,9,13
72:11,15,17
73:18 77:15 94:9
98:6 99:15,19
100:3,10,13
101:2 103:21
107:10 143:14
146:3,9 155:11
156:8 164:9
167:16 197:10
198:6,20 199:16
201:12
221:17,19
230:14 239:20
242:16 246:18

Durmowicz 10:12
12:11 16:21
21:12 26:2,8
114:5,17,18
207:9 208:12
251:15,17
257:21,22
265:20 267:3,5
269:2 270:13
289:22 290:1
319:12,13
325:20,21
346:2,3

dust 216:11

duty 150:12

dwell 28:2

dysfunction 39:2

————————
E
————————

Eakin 230:12

Ear 5:13

earlier 55:8 62:7
90:7 108:18
124:7 133:9
182:15 229:18
231:18 249:2,5
287:2 306:11
309:2 312:1
313:11 314:5
317:7 321:21
323:21 342:14

early 40:11 53:11
57:11,22 84:13
86:10 109:4
110:5 153:14
157:2 161:14
163:7,12
166:8,12
167:9,19
169:15,18 170:4
172:12 173:6
175:14 177:4
178:13 179:1
183:17 215:3
249:22 259:17
288:20

ease 41:22

easier 245:10

easily 35:4

easy 183:4 210:10
219:18 221:15
237:8

easy-to-use 237:20

echoes 286:10

edge 215:11

educate 79:15

educating 235:7

education 110:9
111:10 214:18

effect 27:15 29:9
30:9,17 31:11
43:21 44:15,19
51:9,11,20 54:13
56:3,6,15 57:17
58:3,4,14 62:1
63:22 64:1,11
66:12,16,22
67:11,13
83:13,17
84:6,13,19,21
85:9,10 103:15
116:22 118:17
120:9 121:17
135:5,14
136:13,18
137:11 138:1,10
142:5,11
144:2,21 145:5,9
147:16 149:7,8
168:5 169:9,10
170:7,21
171:12,19
174:12,18
175:2,5
176:18,19
178:6,21
179:1,4,7
180:5,15 181:6,7
186:4,9,10,17,20
187:19 193:1,4
194:2,7,11,21
202:15
206:1,4,7,12
223:8 252:9
253:5
259:15,16,18
273:2 278:4,22
279:5 281:1,10
283:15,16
295:17,20 297:2
300:12 303:22
304:4,7 306:5
307:8,16,17,19
308:13,15,19

312:4,6,16
320:13,17
321:17 322:2
335:6 337:16
338:13

effective 40:9
43:11 45:19 87:2
90:11 108:14
236:19 238:17
239:6 247:5
248:5 268:10
274:6 332:3

effectively 184:1
217:9 292:11

effectiveness 87:6
230:6,9 232:9,17
239:4 275:3

effects 31:13 68:22
84:22 178:1
225:7 228:13
230:10 248:4
262:5 276:13
316:6 338:18

efficacious
261:5,19 266:20
335:9

efficacy 13:18
15:11 16:13
26:13 30:13
31:6,8,20
36:12,13 43:15
46:9 51:1 53:17
59:17
65:10,14,16
83:5,22
115:18,19
116:15
134:14,16,21
138:13 153:5,7
158:22 159:17
161:10
162:13,16,19
163:11,16,18,19
164:19
165:1,9,16,21

166:1,6,10,22
167:5 170:8,11
172:5,9,16
174:12,19
175:1,4 177:3
178:12
179:10,14
180:2,10
188:11,16
189:7,9 191:21
192:20 193:13
195:16 196:1,4
207:5,14 225:19
226:20 227:1
228:6,17 230:4,6
232:17
252:3,5,13,16,21
253:13 255:14
256:9,16,20,21
257:3,11,12
258:4,20 259:11
260:13,18
261:1,10,21
263:3 265:21
266:5,6 268:21
271:4,20,22
273:6 274:12
275:2 276:4,14
280:20,21
281:13 284:1
288:7 290:18
294:9 295:7
304:7,17 306:16
319:19 320:14
322:8,17,18
323:3 330:18,21
332:1,16
333:15,19
334:1,5,19,20
335:1 336:3
341:4 342:2,7,14
343:10

effort 41:9 143:15

efforts 79:12 245:3

Efrati 131:20

eight 120:16

133:19 138:8,11
139:7 197:19
229:22 240:1
272:15 297:14
306:14

eight-minute
328:15

Eighty-five 157:6

either 47:9 53:5,12
70:7 71:21 75:4
77:20 105:20
118:12 122:5
137:20 145:6
164:5 168:1
169:17 176:12
177:1 203:17
211:11,14
239:18 255:6
313:5 325:6

elderly 222:18

elected 86:7

electric 221:11

electronic 150:11
329:16

elements 103:5

elevated 244:16

elevator 216:12

eloquently 184:9

else 84:15 129:7
212:9 235:13,18
242:9 260:11,14
282:12,16

elsewhere 308:16

elusive 294:10

emergency 215:15

emerging 230:15

Emily 218:1,2
244:6

emitted 312:11

emotional 261:13

emotions 262:13

emphasis 109:20
110:9

emphasize 111:4
221:2,15

emphasizing 221:4

empirical 186:11

employed 177:6
347:8,11

employee 347:10

employees
23:4,16,17

employers 24:5

employment 24:9

empower 228:7

empowering
227:21

enable 289:18

encompasses
329:3

encounter 329:9

encourage 24:22
151:21 232:14

encourages 25:19
32:10,17 212:21
213:8

encouraging 288:2

endangering
340:1

endothelial 34:19

endotypes 264:5
271:18 284:20

endpoint 29:4,15
44:17 47:21
48:13 49:5
50:2,21 53:17
55:15 60:22
61:20 146:19
155:17 159:18
164:19 165:9

172:9 174:13,19
175:4,6 176:15
177:3
179:12,14,18
180:2,10 190:11
192:20
208:6,7,11,15,16
209:9 253:15,16
284:5,7

endpoints 47:20
48:9 61:22 62:5
64:10 155:20
162:6,7,8,10,11,
12 163:18
166:2,6
175:1,3,6 176:12
179:10 190:21
191:5,9
195:10,12
206:13
208:9,13,15,19
209:5,6,12
254:3,13 271:13
272:8 285:3
321:5 323:3,7,19

endure 90:18

energy 245:22
246:21 247:11

engineered 35:7

England 54:5
125:11 128:19

enhancing 42:18

enjoy 245:21

enjoying 234:7

enormous 41:15

enrolled 160:17
161:7

enrollment 117:19
157:18 160:7
269:13 317:9

ensure 24:22 32:7
93:17 212:17

311:17

ensuring 35:10 109:21

enter 47:16 101:7 216:18 235:20

enteral 27:4

entered 307:18 329:20,21

enthralling 280:9

enthusiasm 91:2

enthusiast 240:14

entire 36:3 114:13 164:6 174:1 175:12 254:7

entirely 122:1 138:8 325:9

entirety 44:10 67:12

enumerated 333:7

environments 276:21

enzymes 218:12 219:8 244:16

epidemiology 313:9

episode 200:2 315:10

episodes 75:17,18 76:1,3,7,12,15 176:9 199:7,15 204:3 293:14 295:19 296:22 297:9,21 298:4,9 313:17 315:6

equal 192:14 197:11 201:18 230:5 335:13

equally 43:3 119:21 211:3 320:19

equate 312:12

equipment 221:9 236:8

equitable 317:18

equity 32:15

equivalent 98:12 100:1

equivocal 30:15 205:18

error 165:20 166:3 209:13

Esiason 233:4

especially 30:5 58:10 176:6 180:16 202:21 209:11 238:13 263:16 264:21 284:2,5 339:12 343:21,22

essential 83:4

essentially 212:1 257:11 324:19

establish 65:13

established 74:7 79:17 86:10,16

estimate 51:20 55:16 56:3,16 57:16 58:4 64:6 135:5 169:9,10 171:12,21 181:21 183:5 206:6 210:17 312:16 320:17

estimated 37:19 171:17 172:1 176:20 179:8 326:20 328:9

estimates 168:5 178:20 194:4 195:4 222:12

estimating 176:18

et 118:7 229:19 230:12

ethics 23:8,14

Europe 34:3 80:16 105:9 138:5 159:15

European 111:5

evaluable 157:14 255:18

evaluate 51:9 58:22 84:7 286:7 292:9,10 320:21

evaluated 48:8,9 157:8 158:16 160:4,19 161:8 201:12

evaluating 53:17 80:6 271:4

evaluation 1:2 10:9 12:14 259:14 260:6

evening 110:13

evenings 242:20

evenly 178:8

event 50:13 61:10 69:20 70:15 71:1,9 72:22 73:8,15 74:4 76:16 77:5 78:11 79:7 81:6 87:12 88:4 89:14 92:12 104:2 109:13 124:18 131:8 132:7,10 133:12,17 150:17,20 167:21 175:16 196:17,19 197:1,13,17 202:10,13 297:9,10

events 31:17 49:17

52:14 61:14 63:3 69:18,19,21 70:1,2,7,11,13,18,20 71:13,15,18,20,22 72:1,15,16,20 73:22 74:11,14,17,21,22 75:3,4,7,10,15,17,20 76:1,4,7,10,21 77:3,17,19 78:2,6,13,17 79:14 80:4 81:2,5 86:20 87:17 88:11 89:6 90:2 99:15,17 103:3,22 106:11 124:6 130:22 131:13 132:4,8 133:12 188:22 189:1 197:9 198:5,9,13 199:9,19 200:5,6,7,8,17 201:8,21,22 202:2 203:7,11 204:2,3,9,13,17,19 205:1,10 206:21 207:1,2,7 208:18 230:22 294:5 296:15 298:11 303:16 307:21,22 313:2 328:6 341:1

eventual 82:5

everybody 151:7 182:19,21 220:7 235:18 290:8 346:4

everyone 18:3,5 21:18 26:9 94:14 100:17 152:3 287:11 310:18 329:12 330:4,7

331:10,14
341:15

everyone's 151:19

everything 209:12
245:2 258:8
270:6 281:21
282:7

evidence 29:2
31:7,19 44:10
67:13 83:5 92:4
104:9 112:17
194:2 207:13
231:22 252:5,15
253:1,21
255:14,15
256:8,21 257:13
258:4,20,22
260:13,18 261:9
268:21
270:4,14,17
271:4 278:10
279:4 287:22
301:3,11 321:6
322:20 324:2
325:14 330:18
332:1,9 333:4,9
336:1 338:10
339:16,20
340:15 341:5
342:15

evidence-based
132:16

evidenced 206:19

evident 173:14

exacerbation
38:21 60:18
61:2,7 64:14
67:8 75:19
76:8,17 77:4,20
78:5 88:15
121:11 133:18
155:17 175:8,11
176:1,10
191:10,11,15
197:14 204:4

208:16 236:7
296:10
298:10,16 299:5
315:16
318:13,14,19
319:4,6,17 323:3
324:14,16
325:16
326:1,6,7,22
327:6

exacerbation-free
238:18

**exacerbation-
related** 61:14

exacerbations
38:6,17 40:15
43:2,3 48:6
60:13 62:7 74:5
75:14 76:13
82:10,13 85:8,20
87:16 89:3 92:6
124:6 134:12
191:1 225:20
230:21,22
231:11 254:14
260:11 262:5
278:7,13 284:18
296:16 321:14
324:5,6,8,11,21,
22 325:15,16
326:2,4,13,15
327:4,9,14,18,20
328:1,3,4,9
344:15

exacerbation-type
326:10

exact 58:3

exactly 34:9 93:10
107:9 110:6
126:16 240:19
259:19 269:19
312:13 317:18

exaggerated
169:11

examination
170:17

examine 38:22
52:21 190:11
191:21 195:16

examined 51:10
174:9,16 175:4
199:6,9,11 203:9

examining 203:3

example 55:9
58:14 90:19
155:15 161:13
177:16 183:6
187:5 213:4
221:3 254:4,15
271:2 313:14
316:19

examples 224:2

exceed 307:16

excellent 109:2
181:19 253:20
310:17 311:1

except 26:6 66:9
201:21 251:12
310:4 321:17

exception 23:2
28:16 34:8
100:13 153:16
160:9

excessive 306:15

excited 219:16

excites 243:16,18

exclude 25:16
33:17 73:4
137:11 141:14

excluded 33:13,14
52:5 55:18
106:20 107:1
114:8 139:7
148:4 166:22
183:18 200:4

excluding 273:2

exclusion 25:17
157:13 160:13
167:4 169:5,8

exclusively 187:14

excuse 145:14
193:7

executive 2:7
214:15

exercise 219:14
220:22
237:15,17
240:13 243:9,13
244:22

exercising 246:20

exhibit 203:1

exist 132:18

existed 165:2

existing 144:3

exists 40:11
236:18

expand 113:7

expect 92:15 140:9
185:17
190:15,19 191:4
228:13 302:15
312:7

expectancy
37:19,22 233:11
242:3,9

expectation
109:19 164:11
202:21

expected 28:22
66:14 67:1 69:22
156:2 168:14
172:16 175:3
201:9

expel 35:4

expenses 32:14

213:6

experience 60:2
71:19 81:1,19,20
97:12,13,22
105:9 106:15
110:17
111:3,5,14
139:21 164:8
203:17 227:6
237:11 238:4
244:5 246:9
265:19 277:13
296:2,3 302:4
303:1,10 306:22

experienced 74:6
197:22 248:3

experiencing 61:6
64:14 77:14 87:5
259:18

experiment 238:8

expert 24:7 54:3
103:7 131:3
313:9

expertise 128:21
152:17 276:6,11

experts 36:17,21
80:11 131:3
221:6 251:3
285:15 292:7,18
296:2 311:18
313:6 315:9
327:16

expiration 241:9

expiratory 154:4

explain 137:7
299:15

explained 245:8
308:12 337:15

explaining 250:19

explanation
203:16,19
337:15

exploratory
156:16

explore 196:4
197:2

explored 56:4 62:8

exploring 80:13

exposed 68:6

exposing 263:16
303:15

exposure 33:22
68:11,12 112:18
113:3 175:18
196:7 237:12
249:22 287:4

expound 133:3

express 22:3

expressed 145:2

expressing 144:17

expulsion 35:5

extended 216:2

extends 193:12

extension 68:9
86:5 135:21
305:10

extensions 160:6

extensive 33:15
68:22 80:20
81:20 285:18,21
286:5

extra 228:2

extrapolate 237:19

extreme 57:3
215:22 273:1

extremely 108:14
248:5 266:9
288:11

eyes 235:12

————————
F
————————

FAAP 6:13

face 232:15

faced 236:12

facilitates 34:17

facilities 190:14

facing 41:15
235:22

fact 52:11 98:9
104:21 107:1
113:18 119:17
125:15 158:13
173:14 181:12
183:8 209:10
264:13 277:18
286:10,14 287:3
296:21 304:10
305:22 310:8
317:2,5
322:19,20
325:14 337:18

factor 89:8 232:7

factors 41:12
77:15,22 285:22
286:6 301:14
307:14 323:7

fail 42:10 87:3

failed 49:12 62:11
72:14 94:19
95:13,17
96:17,20,22
101:7,17 195:1
199:13

failing 160:1

failure 72:13 82:6

fair 22:1 213:21
273:6 290:5
317:10 324:1

fairly 28:22 87:12
97:15 172:2
188:6 278:4
283:17

fall 72:14 94:11,19

95:11,18 96:17
97:17 98:10
99:5,6,11,13,22
100:2,3 113:17
114:11,15

falling 306:4

falls 72:10,12
98:13 99:18
104:3 113:22
150:10

familiar 215:14
267:19 328:21

families 152:13
219:4 236:3
238:22

family 315:12

fanatic 240:13

farther 215:4

FAS 48:22
52:15,18 53:14
55:16 124:2,21

fashion 41:4 160:3
259:5

fast 111:8 218:16

faster 227:3
245:19

fast-track 155:10

fatal 28:15 74:15
188:22 255:10

fatalities 74:16

father 219:21
222:18 240:16

father's 223:10

fault 171:4

favor 63:12 66:4
135:8,9,13
195:10 206:13
232:2

favorable 139:5
141:13 209:14

307:12

favorably 141:10

favored 54:8 66:9
174:8

favoring 196:20

favorite 225:22

favors 39:9 196:17

FCCP 6:13 7:12

FDA 1:1 2:7
10:3,10
11:3,9,13 12:15
15:4,9,17
16:5,11 18:8
21:6,10,17
22:13,14
23:12,15
25:15,19 26:2,19
27:13,21
32:8,10,17 33:21
48:22 49:3 53:16
54:3 59:11 63:15
68:17,22 70:6
72:19 75:21 77:7
80:17 141:7,8
150:22 151:13
152:6,9,12,20
153:15,21
158:22 159:7
162:21 175:7
179:19 180:20
188:1,13,17
189:19 208:6
212:15,18,21
213:8,14 223:11
248:7 258:19
259:4,7 265:4,7
273:15 287:13
311:15 320:15
333:10,13
334:20 345:21
346:4

FDA's 25:4 58:12
63:20 142:21
158:8 207:15

fears 217:7

feasible 49:2

feature 133:19
143:17
185:13,15

features 55:2
123:16 136:9
285:20

February 155:11
246:14

federal 2:2 12:8
20:8 22:7
23:1,4,5,8,14,17
252:21 270:14

feedback 80:18
142:22

feel 42:9 83:21
105:13 111:12
149:14 193:11
235:15 239:7
240:17 242:8
246:1 258:16
261:4 262:12,16
263:15 273:21
274:20
278:14,17
304:18 323:8
333:9,12,15
334:21 338:4,9
339:11 343:13
344:7,8,12,13

feeling 107:16
108:8

fees 32:13

Feinberg 2:20
20:14

Felix 13:13 36:8
121:18

Fellowship 4:7

felt 105:6 140:7
246:7,22 334:18
338:2 339:16

Feng 11:11 15:12
21:5 153:5
162:21 211:17

FEV1 29:5,16
31:11 33:11,17
38:11 44:11
47:21,22 48:13
50:18 51:1,10,12
52:8,22 53:5
55:21 58:7 59:13
60:8,10,12 61:21
62:6 63:13 64:12
66:3,5,8,9 67:4
72:7,10,14
75:8,11 77:17
79:9 83:10 94:9
95:7,8,9,11
96:17 101:8
102:13 103:11
111:19 112:2,6
113:11,17,22
114:3 115:2
118:10 121:10
124:15 126:17
136:3,5 144:19
155:16,22 156:3
157:7 158:9,12
159:18 160:10
161:20,21
164:20 168:10
169:13 171:16
173:13,22
178:22 181:6
186:4,10 188:7
189:14
190:11,17
191:17 192:4,13
194:16
195:4,5,8,13,20
201:17
203:14,15
206:4,8,16
208:15,22
209:2,15,16
210:2,7 223:15
225:20 231:6
250:6 253:16

254:13 260:10
269:14
271:10,11,12
272:16 278:8,22
279:12 281:9,15
282:20 285:7,21
288:4 300:6
317:1,3,11 319:8
321:13
322:18,22 323:9
326:21 327:4,8
335:14,16,21
344:16

FEV1s 46:12
140:21 148:2
297:22 317:12

fewer 190:22

fibrosis 21:3 24:14
26:15 27:7,18,20
28:3,5,8,13,18,2
2 33:6,9 34:3,22
35:5 36:10
37:7,10,13
38:2,4,8,10,13,1
5,22 39:19
40:1,21 42:8,17
43:19 44:20
46:12 68:4 69:10
72:2 74:4 75:5
80:10,13 81:19
82:16 90:6 97:10
106:6 131:7
153:13 154:21
163:1 176:15
190:19 214:15
215:14 216:1,4
217:4 218:7
220:14
224:12,14,21
225:10 229:8
230:13 231:1,10
233:5,7 234:2,12
235:3 238:3
240:15,21,22
243:3,9 244:8,14
247:17,21 248:9

251:4 254:7 256:12 257:3,7,16 264:13 265:6 269:3,20 279:20 282:20 284:12 289:15 292:16 295:22 296:1 301:16 329:1 330:21 336:14 341:7

field 149:14 296:2

fighting 246:8

figure 45:13 52:2 64:21 65:3 75:6 124:16 173:9 266:8

figures 53:1 173:2,16

files 305:13

fill 150:15 220:16

filled 226:6

filling 226:4

filter 108:18

filtering 108:15

final 52:21 54:10 66:9 152:6 165:20 223:13 244:3 331:2 336:17 341:3

finalization 165:4

finally 35:20 43:7 44:6 67:3 95:9 179:22 189:4 205:13 221:17 246:12 255:8 257:10

financial 23:17,20 24:1,19 25:16,20 32:12,19,20 213:2,4,10,11 214:20 218:4

233:2

financially 347:12

finding 55:20 132:5 137:14 253:13

findings 54:15 65:4,8 69:4 189:8 196:13 202:17 306:16

fingers 222:21

finish 163:18

firm 25:21 32:13

firmly 329:22

firms 25:14

first 29:19 30:6 44:2 46:20 51:12 52:7 55:15 61:10 68:18 69:3 84:11 100:19 103:10 109:14,18 116:20 117:3,16 120:7 122:7 126:7,12,14 131:2,19 135:2,10 137:3 138:1 139:17,22 143:21 157:10,15 166:13 169:3 170:16 173:2 182:9 184:7 190:12 191:10 193:18 201:21 214:9 221:19 222:4 223:6 240:7 246:13 256:6,8,19 258:3 259:8 265:19 267:8 268:11 270:19 272:8 286:18 291:19 297:7 309:4 313:18 315:9 330:16 334:2

335:2 343:21

firsthand 286:12

firstly 44:13 49:10 55:13 66:6 72:4 126:12

fit 122:9 243:1 254:16

fits 91:10 253:17

five 35:22 36:4 44:21 49:16,21 68:5 73:20 74:10 101:3 107:11 157:1 162:10 164:15 214:5 229:2 312:12

five-week 47:6

fix 183:20

fixed 130:6,8,9,10

flash 329:19

flashing 329:18

flat 323:17

floor 258:12

flora 69:14

Florida 2:15 20:3

flow 111:8 323:8

fluid 238:19

Flume 14:12 36:15 81:13,15 92:21 121:1 131:3,6 133:6 134:6,8,18,20 146:6 183:6 235:17 313:8,10 316:11 317:6 323:6 327:21,22 328:18,20

focus 68:16 72:3 79:13 86:20 158:22 163:3 181:1 187:13 189:1 225:12

264:19

focused 68:21 239:10

focuses 140:19

focusing 163:5 228:11

follower 240:12

followup 48:17 51:13 181:20 182:1 334:3

follow-up 121:15

food 1:1 22:20 32:4 33:22

force 267:2

forced 48:5 60:7 64:11 67:8 123:14 275:7 344:19

foregoing 347:3,4

foregoing/ attached 348:6

forest 55:13 57:18 66:5 135:4 192:5 320:10

forget 117:4 139:16,18

forgot 140:7

form 45:8 153:8 318:1

format 80:15

formed 29:6 45:6 46:4 167:1

formerly 222:7

formulate 235:19

formulation 33:19 302:1

forth 333:12

forthrightness 275:13

forties 222:6

fortunate 233:12
  240:17

Forty-four 157:21

forty-one 68:6
  160:20

forum 22:1,11
  345:22

forward 22:6
  53:22 57:10,21
  92:22 100:22
  103:22 104:7,8
  121:21 126:22
  127:2 128:7,12
  171:4 185:7
  189:20 190:9
  218:16 239:16
  253:11 264:14

foster 271:2

Foundation 79:6
  80:14 91:15
  218:4 229:8
  233:5 289:15
  292:16 306:9
  317:13 329:1

Foundation's
  328:21

founder/president
  218:3

fourth 224:8 255:4

Fox 13:19 36:10
  43:15,16,17 84:1
  90:7 92:19,20
  93:7,10,16
  94:16,20 95:22
  96:4 97:3,6,21
  98:4 100:10,20
  101:12 102:7
  103:5 106:18
  108:13 109:11
  110:14,20 112:7
  113:1 117:10
  122:12

123:3,11,15,20
124:13 126:7,10
127:9,14,17,20
128:1,5,9,20
131:1 134:21
135:2 139:20
141:4 143:7,11
145:11 147:19
148:7,20
149:18,22
150:21 249:2,3
251:8 285:17
288:9 289:4,6,13
291:19 296:6
299:16
300:3,14,16,22
306:18 308:13
310:4 311:13
312:8 313:8
320:8,9 327:7

Fox's 186:13

fraction 147:22

framework 153:8
  189:5 205:13
  209:19 252:20
  342:15

frequency 34:18
  70:3 72:19
  131:12 132:3,9
  170:3 200:12

frequent 63:4
  70:1,15,20 72:18
  178:13 197:13
  204:19 231:11

frequently 74:4,18
  75:14 166:14
  179:19 203:18
  315:5

fresh 216:10

friend 240:13
  265:10

friends 218:21
  243:20

Fuchs 48:6 61:3
  62:7 314:11

full 48:21 49:7
  50:1 53:2 54:19
  62:10,18 133:13
  167:7 189:21
  243:12

full-time 222:17

fully 42:10 229:9
  304:12

function 24:15
  26:16 27:8 28:6
  33:10 35:6
  38:10,13,16,18
  39:15 40:15 41:9
  42:20,22 43:2,4
  48:5 60:16 62:5
  77:16
  82:5,9,11,14
  83:12 84:2,13
  85:7 86:17
  89:16,22 92:5
  102:1,5,18
  105:3,22 124:20
  128:17 134:11
  155:1 182:10,16
  190:18,22 191:4
  202:20,22
  216:21 222:5,19
  224:3 231:9
  233:19
  238:11,17
  239:12
  244:10,17
  246:18
  247:7,12,14,17,1
  8 253:17 256:11
  257:2,17 258:6
  267:11
  269:4,13,21
  293:7,10,11,18
  305:11 306:3
  322:14 323:8
  330:20 339:2
  341:8 342:16

functions 186:11
  269:22

fundamentally
  65:15

funding 214:17

Furthermore
  67:13

future 239:16
  240:20 331:18

FVC 45:15
  321:14,18

———————

G

———————

gain 210:2 254:14
  282:11

gained 172:16

gather 80:12
  150:12 249:1

gee 102:22 306:2

gender 66:7 68:3
  285:20

gene 28:6

general 25:9 87:16
  96:12 177:5
  200:8 201:19
  202:9 203:1
  205:12 209:19
  276:9 283:22
  297:22 298:1
  312:22 313:2
  317:12

generally 27:3
  33:20 68:19
  72:18 74:10
  80:22 102:11
  156:15 173:15
  175:3 271:13

generate 132:22

generated 88:9
  132:12

generation 154:5

genetic 28:4 241:2

genetically 37:14

genotype 40:10

gentle 22:4

gentlemen 240:3

Georgia 3:17
20:16

germs 216:19

Gerry 233:2

gesture 294:19

gets 91:1,3 182:19
184:14 271:19

getting 96:8 111:7
121:22 133:13
284:13 297:19
300:8 303:12

GI 28:10

gift 215:18

Gillings 8:8

given 95:6 100:19
101:3 157:11
159:21 161:13
164:11 202:21
238:1 241:10
271:3 290:2
333:13 341:1
342:16 347:7

gives 123:22 132:3
133:20 226:17
271:19

giving 62:14
94:12,13 98:17
102:16 164:17
218:20,21,22
244:4 276:6
289:20

gleaned 279:10

goal 21:22
38:15,21 42:16
170:10 188:18

goals 82:12 213:20
278:6

gone 118:21

Gosh 145:11

gotten 242:4

government 22:8
23:4,16

grade 320:3

graded 98:17

graduate 218:11
219:1

grams 33:22

grand 297:13

grant 23:15 240:5

granted 155:8

grants 24:8

graph 38:12 158:8
186:21 187:17
192:11 211:21

graphing
211:11,15

GRAS 33:21

grazed 303:15

great 1:13 97:20
107:16 115:9
151:1 209:14
213:14 219:6
233:7 245:22
265:10 286:12
289:14

greater 52:11 53:7
59:3 61:18 63:22
64:22 67:2
70:3,11 72:12
79:8 88:5
99:11,18 100:2
101:8 114:11,14
134:8 168:15
192:14 200:3
201:5,6 207:3
282:13 287:1

291:12 298:19
299:22 335:13

greatest 158:11
280:11

greatly 216:4
261:3 332:12

green 53:4 136:2
146:9 184:12,19
185:2,7

Greenberger 2:17
20:12 140:18,19
143:5,8
209:20,21
210:22
263:19,20
271:18
306:12,13
308:5,10
317:21,22
318:8,15,18,21
319:3 332:22
333:1 339:18,19
342:12,13

gross 250:19

group 21:3,14
29:13 30:4,5
50:6,7 59:19
66:6,19
70:4,15,20
71:10,14
73:13,14,16,17,2
0,21 77:3 78:19
81:7 83:19 89:17
99:8,10,12
107:11,12
108:21 115:10
116:10 124:8
130:20 135:14
136:10,12,21
137:2 139:5,6
142:2,8 147:16
149:7,9 159:4
164:2
166:11,14,15
167:18

168:15,20,21
171:20
173:11,14,18
174:17
175:10,22
177:3,9,10,15
178:4 180:1,3
183:7,11,12
184:14 193:12
194:11,12
197:2,16,17,19,2
0,21
198:8,9,10,12
199:18 200:14
202:11,14,16
203:4,12,17
204:20
205:2,3,4,5,7
207:1 210:15,16
226:20
227:13,15,16,17,
18 228:7,15
230:18 262:16
273:12 274:7
290:13 293:5
295:15
297:15,16,17,21
298:2,6,21 307:7
309:14 314:7
319:9

groups 51:17
52:20 63:6,14
66:22 69:7
71:10,18 72:21
74:22 75:7 83:16
116:3 118:12
137:15 148:17
149:5 168:9,17
169:17 173:11
174:5,15
176:11,22
177:17
178:2,8,10
179:11 180:5
181:16 193:9
194:10,16
196:19 197:14

203:15,20
204:10,21
295:12 301:6
307:20 317:10
318:3

grow 216:19 219:1
323:17

growing 305:18

grown 242:2

growth 69:16
146:19 147:8

Grumbine 244:4,6
248:11

guess 102:3,9,16
114:6 117:10
121:21 123:12
170:13 228:9
259:9 278:5,18
281:13 287:20
288:21 290:22
293:18 311:19
312:15

guidance 79:2,21
196:9 265:19
270:15

guide 80:5

guidelines 39:21
40:21 41:6 74:8
79:6 81:22
85:5,6
88:10,13,17
91:14,15
132:12,15
231:18 259:1
315:8 325:12

guitar 223:14

guy 222:17 253:10

_____
H
_____

half 77:16 103:13
147:19 206:3
212:5 219:11
222:14 319:10

327:15

half-marathons
219:11

halfway 280:7,10

Hampshire 1:16

hand 22:10 65:5
137:9 142:7
231:12 248:18
251:20 257:20
309:14 344:1

handle 310:20

handled 125:9
186:3 190:6
205:22

handling 54:7

happen 139:19

happened 107:9
127:13 140:8
181:21,22 182:4
281:3

happens 56:9
125:4 145:16,18
146:7,8,10,15
183:3

happiest 246:14

happy 148:11

hard 110:5 136:20
226:13 227:9,15
320:7

harder 225:12

hardworking
222:16

Harkins 7:12
19:13 276:3,17
334:10,11,22
338:14,15
344:4,5

harmed 183:1

Harvard 8:14 19:9

hate 226:10

haunt 263:7

haven't 18:7
106:12 122:14
123:15 140:6,13
180:21 225:15

having 77:16
103:12 105:10
110:1 111:7
113:16 121:17
122:2 126:18
132:1 137:11
146:20 148:1
150:18 157:22
171:19 173:11
191:3 203:13
225:11,12
239:6,14,16
247:10 249:20
258:15 260:17
262:9 268:13
298:16 310:3
311:11 328:1

Hawkins 9:19 21:2
264:17,18 266:4
281:17,18
287:9,10 334:21
344:5

hazard 61:10

head 35:21 89:1

heading 263:3

head-to-head
117:8

health 3:9,15 6:10
7:8 8:8
20:5,16,17 39:18
42:16 79:22
110:9 150:10
215:20
217:3,13,17
231:3 242:3
244:14 245:3
246:18 248:1
261:8 262:9
263:9 274:17

275:11 276:20
294:7 311:4,5
314:17 329:11

healthier 124:8
217:12

health-wise 247:2

healthy 34:21
219:9,10

hear 26:17 161:9
207:8 217:6
219:5,6 221:6
268:7,15

heard 37:10 82:2
90:17 100:8
117:5 121:1
153:14 154:20
163:21 181:10
183:16 184:20
188:17 202:18
209:1 219:16
221:7,10 230:22
232:1,3 235:9
252:10 270:5
284:11,17
285:13 324:5

hearing 16:18
212:14,18,22
213:15,20
214:6,10 248:14
282:7 347:3,9

heavily 170:19

heavy 180:20

held 21:22 156:7

helicopter 215:13

helicoptered
215:11

Hello 218:2 224:9
251:17

help 36:18 43:4
122:10 147:13
213:16 216:22
217:15 234:5

237:13 238:22
247:22 264:11
265:5,10,14
267:5 271:17
295:4 299:12,21
303:21 306:9

helpful 94:22
113:9

helping 241:7
270:22

helps 110:15
216:8,9 274:5
283:19

hemoptysis
31:3,17 33:12
70:5,14,16 71:4
72:4
74:3,7,11,12,14,
17,19
75:2,3,6,9,13,17,
18
76:2,6,10,12,15,
16,21
77:3,5,8,11,12,1
4,19,21
78:2,7,9,10,16,1
8,20 79:7,22
80:4,8,12
81:6,8,10 86:21
87:11,14,18,21
88:4,6,8,15,18,2
2
89:2,6,8,10,12,1
4 90:2 92:11
130:19
131:4,7,16,18
132:1,18
133:2,4,18
136:19 150:4,8
160:14,15
197:18 198:14
199:8
200:2,5,10,13,15
,17,21
201:2,10,16
202:3,17

203:2,3,5,7,11,1
4,17 204:2,11,18
205:2,6,10
207:2,6 215:7
252:11 278:13
291:2,5
293:3,6,14,17
294:12 295:19
296:3,9,18
297:6,8,22
298:5,9,17
299:3,19 300:13
302:9,18
303:4,22
304:21,22
309:3,4
310:1,2,5,7,9
312:21
313:2,9,13,16,17
,20 314:5,10
315:4,6,10,19
316:14
317:17,22
318:1,3,5,9,11,1
2,18 319:15,16
337:14
338:4,9,16,22
339:22 340:11

hereby 347:3
348:2

hereto 347:11

Herring 8:5 20:21
122:6,7,15
123:9,12,19,21
124:14 126:9
127:8,10,15,18,2
1 128:2,6,10
129:18,22
130:2,6,8,12
184:8 185:11
273:8,9 274:16
276:1 331:14,16
333:7 340:19,20
341:19,20

Herring's 185:12

heterogeneity
277:6

heterogeneous
66:1,15

Hi 20:7

hierarchical 61:22

high 30:3 38:3
50:8 59:2,22
85:15 86:1 103:4
134:2,3 149:2
200:11 218:11
219:1 252:3
262:2 275:16
291:4,10 294:22
340:7,10 342:21

higher 40:3 44:16
63:9 88:2 89:18
98:7 130:19
133:3 149:7
162:1,3 173:12
174:16 197:1,18
198:2,19 199:17
200:13,22
202:13 203:14
204:4 205:1,9,10
262:18 301:13
312:7 334:8

highest 75:11
138:18 158:15

highlighted 55:22
68:17 176:2

highlighting
168:18 179:20

highlights 39:17

highly 60:5 87:1
253:20

Hill 8:9,10 21:1

hindsight 342:18

hint 271:20

historically 258:18
260:20

history 33:12

77:21 107:3
155:6 160:14
200:1,2 263:6
281:2

hitting 222:19

hoc 51:10 61:8
65:4 139:7

Hokey 242:19

holding 35:21

Holm's 166:4

home 91:3 105:1
223:10

honeymoon 215:4

Hong 2:4 12:7
20:7 22:20
331:11 336:22
341:16

honoraria 32:14

hope 233:21
261:12

hopeful 217:16

hopefully 139:11
219:22 223:11
233:8 238:17
250:8

hopeless 262:13
263:10

hopes 83:1 236:11

Hopkins 4:15
20:11 224:11,12
226:2

horizontal 172:17

horrible 303:12

hospital 6:7,15
8:17,19 13:15
19:4,8 191:11
215:7,12,14,16
235:5 315:14

hospitalization
61:13 64:20 78:5

175:9 176:10 297:12

hospitalizations 38:7 191:1 243:14 297:11

hospitalized 299:5 318:9,10,11,13,15,22 319:2,6,15

hour 103:13 212:5 222:14 223:4 244:22

hours 41:20 103:16 215:19,20 219:7 222:13,15 236:4 243:8,11,12 244:21

house 242:17

Howard 5:6 13:19 18:17 25:6 36:10 43:17

huge 58:17 126:18 217:3 243:15 266:6 307:8 333:2

human 34:18

hundred 68:6 72:8 158:15 229:22

husband 215:6 240:15

hydrate 110:12 239:5 246:17

hydrates 35:2

hydrating 40:17 283:14

hydration 238:16 239:11

hydrators 144:4 231:15,16

hygiene 39:7

hyperactivity

46:19 93:21

hyperreactive 115:4

hyperreactivity 73:5 97:14

hyperresponsiveness 27:14 34:8 72:6 106:6 154:17

hypertonic 27:19 40:19 46:17,18 85:3,6,18 154:7 160:15 161:18 222:10 223:8 225:18,19 226:6,8,17,22 227:5,11 231:14,19 232:3,11 237:12 238:9 239:5,19 246:5,16 247:6 282:9 287:12 313:3 316:2,4 325:9

hypotheses 304:2

hypothesis 118:17

hypothesis-generating 156:15

hypothesized 69:11 117:21

hypothetical 55:9 184:13

_____
I
_____

I'd 43:17 49:8 93:4 94:20 102:22 111:18 128:21 134:20 135:18 283:21 291:17 300:14 316:10 345:21

idea 112:14 190:5

243:7,10 259:5 286:11

ideally 109:8 216:8

identical 46:7 65:15 104:2 142:3 312:10

identified 71:20 81:6 162:11 206:2 339:10

identify 18:8 72:6 109:1 123:5 210:2 227:14 228:14 264:11 285:19

identifying 57:1 131:22 210:7 264:10 286:8

ignorable 124:11

ignore 315:6

II 10:9 11:7 12:14 15:14 16:8 21:8 44:21 45:12 67:21 97:8,22 98:6 100:14 117:5 137:12 155:11 191:20 209:2 312:9,17

III 29:11 33:13 36:11 44:4 45:6,10 46:1,3,7 67:21 68:4 72:9 84:14,18 98:13 99:10 100:10,17 137:18 155:13 156:22 158:21 159:1 163:3 201:7

ill 338:18

I'll 47:20 95:21 97:6 113:1 116:21 117:10 122:12 135:22

143:20 181:2,4 258:11,12 269:11,18 320:1 335:5

Illinois 2:21

illness 216:6

illustrate 130:4 167:15

I'm 18:18,19 19:1,3,10,16,19,22 20:4,7 21:2,10,12,15 43:16 93:2 95:20 98:15 99:13 107:14,20 122:12 126:17 129:5 143:8 145:20 149:20 152:9 180:12 218:2,3,6,19 223:5 224:10 237:1 240:8,11,12,13,14,15 243:7 244:6 251:18,20 263:20 264:1,3,18,19 265:18 267:19 268:19 277:10,18 279:17 281:19 286:2 292:18 299:16 300:15 303:7 308:5 319:17 337:5

imagine 229:14 248:6 282:2

immediately 95:18 245:16

immunology 4:7 5:9,13 9:9 18:20 20:20 264:4

impact 31:9 51:19 110:2,6 165:12

169:7 170:10
191:3,17 224:18
226:19 230:19
238:2 252:7
281:6

impacted 169:5
175:13 230:9

impaired 39:5
43:10

implementation
163:10

implemented
80:16

implication 100:8

implications
188:16

importance 39:17
79:16 82:17 92:3
213:15 221:16
232:16

important 32:8
38:21 39:6,12
42:1,22 43:3
44:11 51:18
60:21 103:16
104:6 106:5
113:21 125:9,20
140:2 148:13
150:8 151:20,22
181:18
191:13,22 195:7
197:3 201:21
208:10 212:19
230:22 238:12
239:8,15 241:18
242:7 252:12,18
253:21 260:5
266:9 268:7
270:21
271:7,9,19 290:3
292:8 295:16,21
296:13,18
311:13 317:5

importantly 36:6

52:16 55:4 59:18
71:15 72:10
77:22 89:8
221:10 240:15

impractical 60:20

impressed 336:7

impression 135:16

impressive 86:6
226:9

improve 24:15
26:15 27:8 33:10
39:18
40:12,14,16 41:3
42:16,17 154:22
184:2 224:2
237:22 238:20
240:10 245:19
257:16 259:6
267:10
271:12,13 341:8

improved 40:8
43:22 60:11
61:15,16 64:13
65:22 182:9,16
184:17 190:15
221:21
237:9,14,15
239:12 242:4
253:17 314:17
322:21 334:4

improvement
42:22 51:4,14
58:15,16 83:11
85:7 89:15,16
103:3 112:1,5
114:3 119:17,20
127:6 187:8,9,12
189:14
190:18,20
195:15 206:17
210:11 227:4
235:7 239:10,15
249:15,20 257:1
269:4,20 271:11
278:8 281:5

282:1 283:10
307:20 317:11
326:1,21 330:19
342:16

improvements
37:21 38:1 42:21
43:5 53:6 60:10
67:4,6,7 92:7
126:18 188:7
224:22 242:6

improves 34:21
35:6 92:5 225:20

improving 52:9
57:15 102:6
113:19 119:22
120:2,3,11
134:11 238:17
256:10 258:6
269:12

imputation
54:8,22 55:5
125:14 129:9,18
130:11 176:21
184:21

impute 54:18
170:20 184:17
185:15

imputed 24:3
25:15 55:2 171:6

imputes 52:1

imputing 55:7
184:22

inaccurate 168:6

incidence 38:18
70:11,12
71:8,13,15 74:12
75:6,9
76:2,9,10,13,15,
22 77:10 78:8,16
85:19 87:18 92:5
96:10
99:14,20,21
100:1 106:9

110:4 131:22
191:9 204:4
296:10
309:4,6,9,11
312:21
313:2,12,20
314:4,9,13,18
315:1,19 316:13
317:17 324:22

inclination 284:4

include 24:6 28:9
39:21 54:18 65:2
73:10 78:21 79:6
141:11 142:22
160:13 189:11
213:5 243:14
254:19 328:9
340:22

included 46:5 47:4
48:4,7,18
54:10,21 55:5
61:22 62:5
63:5,8 65:3
68:1,11 77:16
145:22 155:13
156:22
159:11,14 160:5
161:7 169:13
174:2 179:14
199:14
254:13,14

includes 57:10,20
59:14 133:15
175:12 196:13
197:4 202:6
297:10 315:1

including 24:3
32:10,15 43:20
47:13 67:22 68:7
69:4 76:15 79:5
97:7 132:21
188:21 191:9
198:14 200:6
201:9,12 208:21
223:9 244:15

252:10 255:16 301:8 323:3 329:8,9

Inclusion 160:8

Incorporated 214:16

incorporates 185:13

increase 38:18 41:2 55:21 74:13 76:20 92:10 199:17 200:15 237:10,13 238:22 281:9 283:7 309:13,16 323:18 327:5

increased 31:2 39:4 48:2 56:7,10 75:10 78:15,17 113:17 114:2 173:12 200:17 206:21 207:6 237:12 242:3 298:3,19 335:16 337:13

increases 34:16,18 112:19 309:3,17

increasing 75:10 106:8 238:18 242:8 324:2

incredible 218:20 240:19

incremental 37:21 42:22 281:4

indeed 61:16 327:8 328:12

independent 25:10 125:2 319:3

indicate 48:11

indicated 79:11 164:10 165:4

indication 24:13

27:5,6 33:8 132:3 144:6 146:15 154:20 155:6 174:11 192:1 257:18 267:9,13 268:12 269:12 270:20 324:19

indications 143:22 153:22 262:3,4 284:2

individual 60:20 65:14 119:9,10 135:21 288:15 321:16 330:11

individualized 41:13 60:5 286:11

individuals 22:2,4 111:22 331:21 332:11

individual's 23:19 32:9 212:20

induces 34:15 93:14

industry 5:7 23:2 25:4,7,8,9,11 263:22

infected 162:3 222:6 223:1

infection 28:10 39:10,11,13 42:7 82:3,21 83:2 87:15

infections 38:6,17 69:9,10,12 190:22 198:2

infectious 4:9 77:21

infinity 320:6

inflammation 39:11,13 82:4,21

83:3 305:4 306:6 338:10,12

inflated 176:5

influenced 169:2

influx 34:15

inform 52:8 119:3 272:2 313:6

information 23:7 54:9 79:1 80:3 89:17 94:17 97:8 124:1 150:13 186:14,16 193:14 213:4 250:8 255:5 317:7 318:8 326:5 329:2,9 337:20 344:14

information-gathering 32:6 212:16

informative 59:8 109:10 313:1

informed 335:17

infrequent 60:17 74:15

ingredient 68:18 80:21

inhalation 1:7 24:11,12 27:5,9 33:20 95:6 152:22 154:11 232:13

inhale 109:15 216:10

inhaled 26:14,20 27:12,19 28:21 34:5,11,20 35:1 39:22 41:20 50:19 69:12 84:22 85:17 86:8 87:7 91:18 104:22 121:5

154:5,6,8 157:8 161:18 190:12 198:14 201:9 222:10,11 223:3,19 225:5,14 238:9 244:5,11 245:8,9,15 246:3,9,10,12 247:3,6,9,11,13 248:4 290:9 300:21

inhaler 35:14,15,16,18,20 36:1,4 79:13 96:13 109:21 111:7 155:4

inhaling 155:2

inherited 37:14

initial 123:22 173:3 206:20

initially 157:8 198:20

initiated 39:14

initiating 79:19 143:22 144:5

inject 277:7 311:12

injury 305:14,15

input 220:15 323:20

insights 92:20 213:16

insignificant 342:8

instances 213:18

instead 142:14,16 143:2 147:2 181:1 211:12 289:16

Institutes 4:9

instructed 75:16

instructing 315:12

insufficiency 28:10 162:2

insufficient 255:5 339:16

intake 68:21

intend 199:14

intended 60:9 63:7 69:2 167:13 267:9 323:16 344:3

intensity 70:8

intent 49:6 62:9 183:16 334:18

intention 80:16

intent-to-treat 165:14

interaction 65:20 66:21 272:12,22

interest 12:6 22:19 23:6,9,14,20 24:2,20 25:16 32:14 69:9 81:7 118:2 151:16 152:2 180:17 229:5

interested 107:7 347:12

interesting 118:22 119:1 120:12 138:16 280:9,10 305:3 334:2

interestingly 63:20 222:8 223:17

interests 24:6,19 32:15

interim 165:16

interlongitudinal 338:11

Internal 7:14 9:6

interpret 190:10 274:17 275:18 306:1

interpretability 30:8

interpretation 162:18 188:19 307:15 317:19

interpreted 44:10 67:12

interpreting 173:2 186:11 277:2 298:8

interprets 261:9

interruption 22:3

interval 120:16 168:13,19

intervals 66:11,20 190:1 192:6 194:7

intervenes 40:11

intervention 315:17

interventions 236:7

intolerability 114:20

intolerance 262:4 275:15

intravenous 48:7 61:5 318:14

introduce 83:7 90:15 151:17 180:7

introducing 18:16 90:11 146:22

Introduction 12:3 13:7 18:2 33:1

investigate 80:8

investigated 69:13

investigation 338:5

investigational 155:7

investigations 253:3

investigator 69:8 75:5 81:16 200:9 220:10

investigators 75:16 133:16 298:11

investments 24:6

invite 134:20 214:9

invited 25:4

involve 25:13

involved 284:13

involvement 25:17 152:18

involves 24:10

Ireland 159:13

ironmans 219:12

irreversible 238:14 340:22

irritant 305:14 313:4

irritants 112:19

irritation 201:10 302:19

isn't 103:14 119:8 147:16 243:15 258:21 277:21 309:16 317:18

Israel 87:18

Israeli 131:21 313:18

issue 25:3,21 30:2 31:1,18 32:13,20 74:2 88:22

115:6,13,14,17 116:14 119:1 125:10,20 140:16 144:9 148:1 199:3 204:12,15 206:5 213:11 231:12 261:11,14 274:16 280:20 290:14 291:6,17,18 301:14 304:16 327:10

issued 24:21

issues 22:2 26:21 29:22 30:20 31:6 60:2 68:17 79:14 81:5 114:21 125:9 126:2 137:4,5,6 149:9 156:17 162:18 163:9 180:14 196:3 199:10 202:16 207:21 213:17 218:4 244:16 252:7,11 255:7 262:9 274:7 275:6,10 290:2 294:13 295:7 297:6,8 305:5 311:6,15 326:8 329:11 343:22

ITEM 12:2 13:3 14:3 15:3 16:3 17:3

iterations 58:2

it's 51:18 98:17 109:2 110:5 115:5 120:9,16 124:7 130:9,10 134:6 135:19 140:3 144:10 146:12 150:22 172:2 210:6,10

212:3 219:18
221:13 226:13
230:19 237:9
256:17 262:6
267:15,16 271:6
275:12 283:4,13
284:6 286:3
291:17 293:8
301:4 304:2
306:20 312:4
315:10 317:9
320:7 323:10
324:1

ITT 48:18
49:2,3,18,19,20
50:3 52:16 53:16
54:18 55:7,22
56:5 57:9,17,19
59:7 61:7,17
62:14,19 161:7,9
166:9,11 167:1,6
168:1 169:4
172:20 174:1
175:12
189:10,21
192:2,9 193:5

IV 64:15 328:4,6

ivacaftor 28:17
40:5,6 238:4,10
254:6 314:9,21

I've 143:19

J

Jacksonville 2:15
20:3

Jacoby 3:6 12:4
18:3,11 20:4
21:18 26:1
32:1,3 93:1
94:2,17 95:14,20
96:3,6 97:4,20
98:15,20,22 99:2
100:4 107:5
111:17 112:16
114:5,17 116:18

121:14 122:6
130:14 139:12
140:18 143:4,18
149:16,20 150:1
151:7,12 152:15
207:17 209:20
211:9 212:4,12
214:12 217:22
220:5 224:7
229:1 232:21
234:19 239:22
244:2 248:11
251:8,21 256:4
257:21 258:2
261:6 263:19
264:17 265:17
267:3 272:5
273:8 274:14
277:9 278:2,16
280:18
281:16,19
282:17 283:20
287:9,19 289:22
290:17 296:5
297:4 299:7
301:22 302:6
304:15 306:12
310:11 311:20
312:19 315:21
316:9 317:21
319:12,18 320:7
321:11 322:15
325:20 326:17
328:14,17
329:14
331:5,7,13
332:5,14,22
333:5,8,17,21
334:10,16
335:3,19
336:5,11
337:2,7,21
338:6,14,20
339:3,7,13,18
340:5,13,19
341:3,18,22
342:3,12

343:3,6,15,18
344:4,10,17,22
345:10,16

James 9:5

January 1:11

Jeff 19:10 334:17
338:7 344:11

Jeffrey 9:12

Jenkins
214:11,13,14
217:22

Jersey 5:11,12,15
18:19,21

Jim 20:18 332:6
340:14

job 242:17

John 7:5 19:16
333:22 338:21

Johns 4:15 20:11
224:11,12 226:2

join 346:3

joining 229:7

Jonathan 245:6

Journal 54:6
91:22 125:11
128:19 230:13
264:3

judgment 298:13

jump 123:3 315:14

jumped 245:11

justified 170:2

K

Kathryn 2:12
19:22 333:11
339:8 343:9

keen 185:9

Kelly 4:6 19:19
333:18 339:4

343:16

key 26:21 42:16
48:9 60:13
155:12
162:7,10,18
166:5 225:9
285:20 321:4

kids 136:18 137:19
138:21 148:4
219:1,4 222:18
302:9

Kimberly 10:16
15:7 16:14 21:9
152:9

kinds 184:11

Kingdom 159:12

kit 27:13 154:15

knew 221:18
329:12

knowledge 87:16
248:3

known 28:1 30:22
71:21 73:1 89:7
134:1 154:12
157:9 159:20
164:9 213:3
313:12

L

------

label 33:14
73:3,10 81:10
145:7 146:2
157:3 198:22
260:16 267:20
272:2,3 289:17
309:12

labeled 154:18
221:20 267:7

labeling 253:8
265:21
266:2,15,17,22
267:2,19

268:4,7,8 335:11

laboratory 19:20
69:3,5,6

lack 29:9 66:20
158:17 179:21
193:1 195:19
196:1 294:15
307:6 332:9
340:7 345:2

lacking 228:20

ladies 240:2

lady 222:4

laid 270:13

language 123:9

laptops 212:6

large 56:19 68:4
72:11 74:10
98:13 118:8
124:5 136:13
144:10 147:17
161:3 222:9
278:4 284:3
316:4 324:9

larger 98:11
136:14
147:10,16 188:9
203:21

largest 46:4 98:10

last 53:5 54:6
126:17 145:4
149:16,18
188:13 195:16
222:5 225:17
227:20 250:11
251:1 264:4
314:22 328:2,5

lastly 66:7

late 114:10

later 26:22 30:1
45:7 70:16
106:11 156:18
161:10 201:3

207:10 215:6
220:4 262:22

latter 84:18

Laughter 152:6
267:21

lavage 301:20

laws 23:6,9,14

lay 180:20

laying 270:10

lead 41:12 69:12
90:14 116:7
236:18 237:2
291:12 293:15

Leader 10:13

leading 39:14 42:6
60:15 200:7
202:13

leads 28:7 39:3
43:10 236:21
247:16 275:5

leaps 241:15

learn 111:5 266:7

learned 62:22
111:10 273:18
275:17

learnings 109:11

least 47:8 48:17
58:5 61:4,6
64:14 68:12 70:3
71:2 87:22 99:7
106:19 109:9
112:18 114:21
145:3 146:12
165:15 168:15
173:22 181:6
196:17,18
208:17 225:22
249:1 261:5
276:12 304:17
305:12

leave 212:6 236:12

leaving 49:17 50:6
55:10 56:17
57:11,22 109:14
112:12 124:7

led 70:19 73:19
203:14 317:9
342:20

left-hand 56:11
111:21 136:6
138:22

lend 188:4

less 33:11,17 51:6
61:15 63:21 64:2
66:10,16 68:20
74:10,21 77:17
79:9 84:21
87:4,14 99:12,22
104:3 113:18
115:5 118:17
125:1 142:18
148:2,5 168:21
170:20
187:15,21 192:2
201:17 202:7
203:1,4 207:5
208:16 225:8
226:6 234:10
246:20 269:15
282:8 307:12
312:14 315:20
316:18 319:10
322:8 327:11

lessen 110:10
278:7

lessening 38:20

lesser 135:14

let's 18:16 38:22
69:3,18 72:4,15
73:12 74:3 83:9
86:19 88:22
138:20,21 152:1
193:17 231:12
255:8 258:2
290:19 293:10

319:18 331:13
337:2 341:18

letting 220:3 240:7

level 100:2 165:21
252:3 262:2,18
267:8 275:16
289:8 295:1
301:18 307:9
312:7 340:7

levels 103:16
301:6

liaison 79:20

lies 173:15

life 37:8,19,21
90:19 175:9
176:13,14 177:1
191:2,12 215:11
216:1,3 217:1
218:21 219:21
221:13 225:1
226:3,9 228:8,18
231:2 233:11
234:3,7,9,11
238:21
240:4,5,10,19
242:3,4,5,8,13
243:5 246:2,8,15
248:6 260:12,21
284:12 339:22

life-changing
218:20

lifestyle 91:11

life-threatening
270:20 271:6,8
339:22

light 73:8 124:4
191:6 209:14
214:8 272:14
282:21 283:6

likelihood 164:12

likely 30:10 46:1
52:18 57:16 58:5
59:19 70:8 84:21

99:16 103:21
109:16 122:21
124:10
125:4,19,21
140:5 166:19
169:20 198:13
203:1 283:13
288:11 313:22

Likewise 32:17
213:8

limit 79:10 105:8
168:12,18
207:20

limitation 79:11
272:1

limitations 226:10
268:13 269:6

limited 23:9 26:14
77:12 195:12
206:15 305:19
319:20,21

limiting 52:18
79:17

limits 41:21

line 53:1 119:4
135:8 141:20
142:1,8,12 146:7
172:22 173:15
184:19 185:2
187:6 192:17,21
211:7 231:8
249:13 301:15

lines 52:2 53:4
119:6 127:15
184:13,15 185:3
197:12 211:1
266:4 273:15

link 302:20

linked 38:19 43:5
169:21

liquid 34:16 39:3
40:18 41:2,3

LISA 348:2,12

Liscinsky 18:9,10

list 145:12 166:5
285:21 286:1,3,6

listed 165:11

listened 213:22

listening 278:20

lists 153:20 162:5
189:18 198:4

literal 277:3

literature 126:1
154:11

little 31:12 84:15
102:15 125:12
128:7,18 150:11
181:3 184:10
187:18 192:22
211:8 222:3
224:17 225:8
242:8 245:19,20
246:1 253:9
259:3 265:19
316:11 322:6

live 218:10 219:21
242:7 310:16

lived 218:18

liver 244:16

lives 215:18
218:21 220:1
228:2 251:3
265:1 322:21

living 233:12
234:7,11 244:8
264:22 265:6
276:20

load 250:15

lobectomy 215:9

local 68:22

LOCF 176:21

locked 330:5

lodging 213:6

London 104:17,18

long 28:2 59:20
60:1,15 100:18
107:22 108:12
150:20 185:19
208:16 218:10
226:11 305:10
324:8 344:14

longer 56:5,16
121:7 140:14
171:2 208:17
209:4 217:1
225:1 245:20
248:15 266:21
283:2 284:17
289:21 305:8
338:11,17 340:2

longitudinal
288:1,7,9,18

longitudinally
54:20

long-term 293:15
295:20 296:19
306:5 342:21

lose 194:15 282:15

loss 28:6 186:13

lost 56:8,13 57:4
58:18 181:20
182:1 282:14

lot 82:20 97:13
110:14 111:9
116:11 125:22
131:6 183:20
187:2 219:5,18
224:20,22 228:1
234:2 242:15
247:3 251:4
252:10
273:18,22
296:2,3 303:3,12
305:6,12
310:13,16 311:2

334:3,4 336:16

lots 144:12 329:9

love 219:20 220:2
244:9
274:4,10,11

low 73:7 91:9
96:11 204:11
312:3 314:3
317:1 339:2

lower 40:1 57:16
61:12 63:1 64:3
70:13 71:8,16
110:3,4,5 158:7
160:10
168:12,18 198:1
202:11
203:13,14
263:13 297:22
309:9 343:1

luckily 148:4

lumen 34:16

lunch 22:18 91:2
212:5,11

lung 34:12
35:2,6,8,11
38:9,10,13,16,17
39:6,12,15,18
40:14 41:9
42:16,20,22
43:2,4 48:5
60:15 62:5 68:22
77:16
82:2,5,9,11,14,1
5 83:12
84:1,12,13
85:2,7,12 86:17
88:9
89:7,9,16,21
92:5,17
102:1,5,18 105:3
124:20 128:17
131:9 134:11
201:13,17
202:1,4,20,22

205:8 209:4
215:9,10 216:20
217:13,17
222:5,18 224:2
233:19,22
238:11,14,17
239:12 244:17
246:18
247:7,14,17,18
253:17
269:4,13,21
293:6,9,11,17
299:11,12,22
300:2,8,12,17,22
301:3 302:14
305:11,20,22
306:3 314:17
322:13 338:10
339:2

lungs 38:5 147:10
215:8 216:14
217:11 223:7
233:18 234:5
244:20 245:10

_____ M _____

macrolides 40:1
85:3

magnitude 179:6
187:13 194:15

main 29:1 31:5
52:13 74:14
143:15 188:21
225:17

Maine 245:5

mainly 52:14
64:10 83:18

maintain 39:6
41:9 86:17
124:22 165:19
245:3 247:18
248:1

maintained 54:14

maintaining 42:20

maintenance
238:15 336:13

**maintenance/
treatment** 257:7

major 71:12 87:9
109:12 179:17
196:12 199:9
231:3

majority 74:11
75:3 201:8
202:19 216:5
292:15 296:15
303:18

manage 110:10
132:17 133:21
277:19 311:10

manageability
292:19,21

manageable 81:9
87:10 292:3,5,13
340:1

managed 250:3
328:22

management 2:6
24:14 27:6 33:9
42:15 74:7 79:22
154:21 163:1
230:10,11
232:18 234:12
257:15 269:19
311:19 318:6
341:6

managing 9:8
59:20

mandatory 73:4

manifestation
88:15

manner 55:3
330:14

mannitol 1:7
24:11,17
26:14,20 27:1,12

28:21 33:5,20
34:6,9,12,15,17,
21 35:2,8,9,11
41:1 43:18 44:22
45:11 46:18,21
47:10 68:19
69:12 71:20 72:5
80:21 86:22
91:19 93:5,7
94:5,6,7
96:19,22 97:12
100:19 101:4
106:10
114:12,19,22
115:8 117:9
120:11 121:6
137:10 141:21
142:2 152:22
153:1 154:10,11
157:9,11 158:19
159:21 164:14
190:13 198:14
206:20
221:14,21
223:6,20,21
226:19
231:13,20
232:2,10,13
244:5,11 245:8
246:9,11,13
247:3,7,9,11,13
248:4 250:2
256:9,15,17,22
257:6,14 258:5
290:8,9,20
325:17 326:21
332:16 335:14

mannitol's 71:22

marginal 335:7

marked 112:1
153:13 158:12
199:5

marker 109:4

market 218:18

marketed 154:14

marketing 289:2

markets 34:5

marriage 215:1

married 219:2,21

Marschall's
317:13

Marshall 229:3
232:21 236:21

Mary 6:13 18:22
336:6 337:5,8
345:11

Maryland 4:10,16
9:21 347:19

Massachusetts
8:20

massive 74:14
78:9,10,17 79:7
87:13 88:4,6,18
89:11 131:16
133:2 280:7
313:16

matching 54:22

material 179:13
278:19

materially 165:12

materials 94:6

mathematics
320:8

matters
24:16,17,20

maximally 45:19

maximize 65:17

maximum 51:11

may 24:6 25:21
26:5 32:12 34:13
45:21 51:17 52:4
54:2 58:15 64:8
76:4 90:10 91:5
106:10,11,18
108:7,8 116:10

117:11 120:6
137:7 144:22
145:1,12
155:20,21 168:6
169:1,8
170:13,16
171:7,9
175:13,20 176:5
178:22
179:1,7,12
181:19 183:1
184:22 194:13
203:16
206:11,12
213:2,5 214:9
226:8 241:17
249:10 251:11
253:19,22
259:2,10,19
260:4,9,10,11,12
,13,18 265:9
266:5 270:19
273:2 276:11
277:13 279:9
281:10,11
282:6,15 289:13
298:16 304:3,6
305:14 306:7
307:3 309:22
317:3 320:16
321:2 328:21
331:20 337:16

maybe 100:8
107:16,20
144:21
268:19,21
271:13 278:18
281:14 295:4
299:12,22
306:10 308:12
314:18 317:16

MD 1:17 2:17 3:6
4:6,12 5:6 6:5,13
7:12 8:12 9:12
10:5,12,16
12:4,11 13:13,19

14:7,12 15:7
16:14,21

mean 64:4 72:14
95:18 102:11
103:3,19 113:22
114:2 121:19
126:12 128:3,11
130:9 144:20
147:21 148:10
161:20,21
168:21 186:9
227:8 230:1
250:6,9 253:11
283:7 285:4
289:13 300:11
302:12,13 303:2
314:3,13
315:13,14 342:6

meaning 49:22
60:18 169:15
270:17

meaningful
44:2,19 55:3
58:1 67:4 75:22
83:15 85:13 92:7
190:20 191:5,18
195:8,14
206:4,17 207:7
209:4 232:8
252:10 254:2,12
327:12

meaningfulness
321:10

means 44:9 56:17
57:4 114:1
115:15 124:14
144:14 181:15
253:14

meant 184:5 197:5
253:12 298:12
308:3

measurable
283:16 285:9

measure 48:17

53:5 60:13 72:7
155:14 175:9
176:13 190:17
191:15 285:7
301:6,18 324:7

measured 38:11
72:10 95:7,8,10
113:11 122:18

measurement
166:13 285:10
314:11

measurements
94:9 128:17
165:10 166:21

measures 48:14
49:3 69:5 181:10

measuring 260:9

mechanism
39:6,18 67:6
71:22 124:9,15
126:4 127:22
129:19 286:14

mechanisms
120:10 323:20

mechanistic 302:9

media 22:12,15

median 37:19
74:20 89:16
216:2

medians 250:7

medical 5:12 8:14
9:14 13:12,20
14:8,15 18:19
19:9 36:9 37:2
40:11 43:17
67:19 79:20
152:9 217:14
241:8 245:5
261:15 318:6,7

medically 262:20

medication 83:3
85:16 86:2 92:16

137:6 139:16
144:1 172:15
227:19 235:15
260:1 276:12
285:16 290:6
296:21 311:17

medications 84:9
85:2,22 110:19
144:5 150:7
217:16
220:16,21 226:4
228:14 233:16
236:5
241:4,8,14,19
247:21 264:11
276:7

medicinal 34:1

medicine 2:18,20
3:8,10
4:13,14,15
5:8,10 6:9
7:13,14 8:16
9:6,7 13:14
14:14 18:18
19:14
20:11,13,14,19
27:3 91:22
224:10 275:8
289:20 306:3
340:3

medicines 244:21

meet 190:8 193:22
195:1 237:9
253:18 255:7,14
259:1 272:7
333:19 339:5

meeting 2:1 3:1
4:1 5:1 6:1 7:1
8:1 9:1 10:1 11:1
18:9,13 21:21
22:1,6,11,15,17,
21 23:11,22
24:16 25:6,8
26:3,4,11 32:16
49:18 141:7

155:11 156:7
191:20 209:2
213:7 248:15
251:10 281:6
329:17 346:7

meetings 32:8

meets 196:9 209:7
262:19

member 260:22

members 2:9 3:3
4:3 5:3 6:3 7:3
8:3 9:3,17 10:3
11:3 18:2
22:9,12
23:2,3,12,13,22
24:19 25:1,12,13
28:3 151:21
152:16,20
345:18

mention 304:19

mentioned 30:22
31:16 87:20
124:7 125:11
161:18 191:16
269:3 271:18
294:11 295:21
335:12

merely 178:4

merited 336:9

message 334:6

messes 115:18

met 72:12 158:1
192:16 331:22
333:12 336:10
337:6,9

meta 332:20

methacholine
27:13 154:17

method 54:7 57:3
64:4,7 87:2
128:8,15 146:21
163:14

164:16,22
165:6,7,8 170:18
171:9 172:5
176:17,21
181:17,19
311:17

methodology
50:22

methods 36:13
125:14 170:20
184:16

Mexico 7:16,17
19:14

Michelle 7:12
19:13 338:15
344:5

Michigan 218:3

microbiology
69:4,15

micrometers
35:10

microphone 337:7

microphones
329:18

Mike 224:10

mild 70:7 74:12
75:4 77:18 78:3
131:17 132:8
134:9

milligram 29:7,8,9
36:3 44:1
45:10,18,21,22
49:13 94:14
95:12 98:8
122:11
137:18,19 149:7
158:5,11,13,14,1
8,20 159:6,8,9
312:12,13 343:2

milligrams 27:9
34:2,12 35:12,13
44:22 45:3,16

47:10,17
93:11,19 94:8
95:6,7,8,9 96:18
98:17 137:10
146:11 155:1
157:16,19
158:15 196:7
250:5 256:10
257:1,15 258:5
307:7 309:15
312:2,5,9 330:19
341:6

milliliter 192:14
282:1,11

milliliters 30:19
146:20 186:6
187:6,9,14 188:7
190:1 194:8
200:3 210:12

millions 82:19

MILTON 304:6

Minasian 118:7

mind 36:7 207:11
232:14 274:9
277:18 285:2
313:13 323:16
324:7 332:11

mine 180:17
223:12

Mineola 6:16

minimization
79:12,21

minimize 38:16
79:13

Minneapolis 7:10

Minnesota 7:9,10
19:18

minor 24:4 302:17
315:7

minority 182:3
188:8,9

minus 115:2,5,16

141:1

minute 91:1

minutes 36:4
97:19 101:4
152:20 174:21
214:5,7 218:14
221:7 222:13
223:4 226:12
229:22 230:2
232:4 243:8
246:3,5 247:4

mirror 60:9

mirroring 205:11

misleading 342:20

miss 140:6

missed 55:6 93:5
175:19

missing 30:3 31:9
44:17 52:1,3
53:18
54:4,7,9,18
55:1,2,8,9
56:1,7,11,15
63:17 122:17
124:9,10
125:19,21 126:3
127:10,19,22
128:2
129:19,20,21
130:1 158:2
163:16 168:2
169:2,14,15,20
170:1,10,19,21
171:6,13 172:6,7
173:7 174:2
175:18 176:6
180:16 186:3
190:6 194:22
205:19,22 206:5
252:7
273:12,19,20
274:2 334:3,13

missingness

127:12 334:5

mistake 278:9

misunderstood 123:4

MITT 49:1 167:1,3,6 168:1 169:4

mixed 48:14 125:18 165:9 181:10 274:3

mixture 54:12 55:4,21 56:12,22

mL 58:15,16,20,22 142:11 168:10,15,17,22 171:17,21 172:2 173:22 177:16 179:7

mLs 51:2,4 53:7,8 55:5,11 56:1,15,16,18 57:4,7 58:5 63:13 74:10 83:13,14 84:14,19 85:9 89:16 139:3,6,9 144:14 147:3 148:18 149:15 194:5 195:4 206:3 210:3 320:18 321:13 322:5

MMRM 48:14,16 52:1 53:21 54:21 55:15,22 64:4 165:10 168:8 169:13 170:8 174:11,20 176:17 178:20 189:10

mobility 41:22

mode 65:21 72:1 81:4 237:14

model 48:14,21 52:1 53:21 55:4,7,21 56:12,22 125:18 129:19 163:11 165:9 168:8 176:17,20 181:10

modeling 126:1

models 54:8,12 122:9 126:5,21

moderate 50:18 70:7 75:4 77:18 78:3 251:21

modes 238:6

modest 37:22

modifiable 331:4

modification 334:22

modified 166:9 167:1 189:10 268:1 334:18

modulators 238:5

Moira 220:9

moldy 216:13

mom 223:14 241:10

moment 118:19 266:3

Monday 220:17 243:7

monitor 88:11 92:12 276:7 323:12

monitored 69:5 338:17

monitoring 79:3 150:7

month 46:9 78:14 220:20 243:11

months 51:9,15 86:8,18 88:1 198:1 200:4 221:19 233:17 289:17 305:9 309:5

morbidity 38:1 43:6 48:2 153:14 231:1

Morgan 18:9

morning 18:17 26:8 33:2 110:13 129:5 152:8 182:15 188:13 220:17 223:18 230:5 231:19 312:20

mortality 38:2,20 43:6 48:3 153:14 216:21 231:2

mostly 37:17 278:8

motivated 150:6

Mountain 215:5

mouth 35:20

move 73:12 87:11 196:6 199:4 216:15 221:22 253:11

moved 343:12

movement 291:13

moving 46:3 47:19 63:11 65:10 151:17 173:9 174:22 177:2

MPH 8:12

MTT 46:21 47:5 49:12 62:12 72:9,11 73:4,7 79:21 87:3,7 91:20 97:17 99:16,19 100:3,6

101:17 102:19 106:15 157:11 159:21 160:1,20,22 161:4 199:14 204:16 250:4

muciliary 217:16

mucociliary 34:21 39:5 40:17,19 41:3 42:18 65:22 120:11 259:6 285:3 323:22

mucoid 162:4

mucolytic 27:22

mucolytics 144:4 154:6

mucus 27:17,22 34:17 35:3,4,5 39:4,7,9,14 61:15 216:8,14,15,17,22 217:8 218:15 233:18,20 244:20 245:10,14 283:3 302:14,15,21

Mullins 3:13 20:15 130:14,15 133:3 134:2,7,13,19 135:1 261:6,7 266:12 274:14,15 276:16 287:19,20 288:21 289:5,7 290:21,22 294:3 310:11,12 332:14,15 340:5,6 342:3,4

multi 46:8

multi-organ 28:7 38:4

multiple 30:11

37:22 54:8,22 55:5 94:13 129:9,18 205:20 239:8,16 243:14 252:8 254:3,12 301:14

multiplicity 166:3

mutation 39:1

mutations 28:5 37:11 241:2

mycobacterium 222:8

myriad 236:13

myself 245:11 253:10

N

narrowly 44:17 63:17

Natalia 1:19 347:2,18

nation 262:10

national 3:15 4:9 20:17 54:3 214:16

Nationwide 6:7 19:4

native 240:11

natural 284:4

nature 41:8 44:8 168:4 169:17 177:5

NDA 1:9 26:13 33:5 45:18 156:13 176:1 189:9

nearly 66:4

Nebraska 9:10

nebulization 40:22

nebulized 41:17

220:17,19 221:8 230:3

nebulizer 41:21 232:4 301:9

nebulizers 42:3,5 244:21

necessarily 109:9 128:3 209:9 304:4 307:6 317:18 339:2

necessary 155:18 236:8 239:19 284:18 345:14

negate 84:2

negative 30:14 114:1 158:14 164:14 168:22 205:18 248:4 295:20 297:2 335:14

negligible 315:20

neither 64:17 162:6 347:7

Nemours 2:14 20:2

neonatologist 8:15 19:7

net 231:22

nevertheless 55:19 59:10 66:15 112:2 136:14 321:1

Newark 5:12 18:19

newborn 8:16 37:17

news 224:20

NIAID 19:21

nice 109:4 121:10 122:22 276:14

nights 215:6

nine 87:19 131:22 199:1 214:6 233:17 244:3 314:4

nineteen 72:8

nobody 319:15

nominal 326:16

non 25:6 34:14 58:15 116:6 122:18 124:10 186:4 188:21 190:20 291:9

non-clinical 69:1

non-conservative 141:13 142:20

none 65:19 77:22 170:14 195:11 200:11 206:14 286:1,7 301:22 318:10

non-employee 32:11

nonprofit 214:17

non-responder 172:7,12 173:7 174:3

non-responders 286:22 287:7

non-spirometry 179:12

non-tolerators 116:11

non-virgin 283:14

Non-Voting 2:2 5:4 9:17 10:3

Non-Voting)(cont 11:3

nor 162:7 347:8,12

normal 38:14 39:6

202:20

normalizes 103:13

normally 111:1 319:10

north 8:9,10 20:22 138:5 215:5 307:9,13

Northern 215:12

Northwest 221:1

Northwestern 2:20 20:14

nos 331:11 336:22 341:16

Nose 5:13

notable 29:18 115:2 205:4

notably 31:17 74:15

Notary 347:1,18

note 27:11,17 84:15 113:21 161:20 173:2 177:12 190:7 191:13 197:3

noted 25:18 68:22 70:6 72:19 75:13,21 156:11 166:12

notes 348:5

nothing 91:16 129:7 137:17 209:12 214:20 281:22 282:10

notice 145:22

noticed 238:5,11

notion 149:11

novel 33:19

November 155:8

nowadays 37:17

38:13

NRC 54:6,12,16

numeric 178:7

numerical 118:14
174:7,10 176:3,4
177:12,17,22
179:20,22
192:18 309:19

numerically 63:12
107:2 137:2
173:11 179:4
187:20 191:7
195:10 196:17
206:13

numerous 164:21

NY 6:16

_____
O
_____

Oak 1:14,15 26:9

OB 11:8,13 15:15
16:9

objective 26:12
61:1

obscure 181:11

observation 26:5
53:22 57:10,20
126:21 127:2
128:6,11 129:17
171:4 189:20
190:9 199:3
318:7

observations
181:14

obstruction 28:9
39:7,8 82:4,18

obtain 89:21

obtained 33:16
126:6 164:9
257:9,19 330:22
336:4,15 341:9

obvious 183:6

obviously 94:13
106:21 118:3
119:8 123:6
126:8 132:6
138:12 139:14
142:17 143:12
146:15 227:17
285:8 306:19
314:6 320:9
327:19

occasion 114:15

occur 92:13 143:9
169:20 198:2

occurred 77:19
78:11 165:4
167:16 197:9
198:5 201:5,22
202:3 205:3
298:9 342:5

occurrence 61:4
130:19,21
131:17 133:4
175:16 197:18
204:11 291:5,10
340:11

occurring 70:3
75:18 150:17
166:14 204:18
205:6 299:6

occurs 89:2 200:11

October 54:6

ODE-II 10:9,14,18
12:14 15:9

offered 86:4

offers 91:9

Office 2:7 10:9,10
11:8,9 12:13,14
15:15,16 16:9,10

officer 2:2 12:8
13:20 20:8 43:17
152:9 347:2

off-label 153:22

offset 130:9,10

Oh 96:3 105:5
116:20 140:7
275:5 301:2
308:7

Ohio 6:9,11 19:5

old 92:14
177:11,20 202:7
218:6 222:5,17
233:5,11 244:13

older 24:15 27:7
33:10 46:12
91:20 144:13
154:22 157:7
177:10,11,21
192:2 203:21
241:9 256:11
257:2,16 258:7
267:10 269:4,20
290:18 330:20
341:7

olds 76:22

Omaha 9:10 20:20

OND 10:10,14,18
12:15

ones 96:17 103:2
107:4 233:12
284:10 298:10
309:22 326:12
340:3

one-week
157:17,20

one-year
155:16,18 326:4

ongoing 149:13

onto 300:12

onwards 52:19

open 16:18
22:1,11 26:4
35:16 145:7
146:1 157:3
198:21 209:8

212:13,18,21
213:15,20,21
214:6,10
221:18,19
248:14 251:10
260:16 289:17
309:12 345:22

opened 155:7

opening 12:10
26:2,6 302:21

open-label 29:2
45:4 47:16 68:9
78:11 86:5,14
145:15,19
146:13 160:5
198:18 199:3
200:16,18
245:13 309:7

operate 241:3
252:20

operating 209:19

opinion 148:11
249:11,22

opinions 21:21
213:19

opportunity 33:4
37:6 89:21 120:1
151:14 214:14
229:3 234:22
241:20,21
245:7,12 287:3
302:17 333:13

opposed 93:19
102:2 123:6
208:22 317:4

opposite 58:17
296:22 306:1

optimal 35:7 43:8
285:19 291:14

optimized 35:10

option 91:9
92:13,15 226:17

234:16 236:18
238:19 239:5
243:17 280:5

options 42:11,14
91:7,8 121:19
217:19
234:3,15,17
238:22 239:17
241:4,11,14,18
242:2 243:21

oral 24:12 213:1
328:9

oranges 290:14

order 12:3 18:2,14
30:7 90:20
110:19 117:11
144:5 167:22
273:22 308:2

Oregon 3:9,11
20:5

organ 38:5 197:12

orient 192:12

original 81:22
124:22 131:15
200:22 327:2

originally 114:9
194:17 305:13

orphan 29:1 37:15
44:9 46:5
67:10,15 68:5
155:8 196:8
255:16,18 284:2

oscillating 283:4

osmotic 27:3 34:13

others 170:14
229:11 239:6
241:17 293:7
339:14

otherwise 269:21
347:12

OTS 11:9,13 15:16

16:10

ourselves 18:16
241:21,22

outcome 32:16
98:14 139:5
144:17
155:14,16
164:14 178:22
182:12,21
236:19 260:10
272:13 273:5
307:11 347:12

outcomes 156:5
182:6 190:16
191:18 195:8
236:22
237:1,3,14 273:1
284:9,10 344:15

outline 26:20 36:8
155:5 188:14

outlined 39:21

outlining 26:19

outside
139:14,21,22
175:5 250:18

outsourcing
287:14

outweighs 23:19
89:22 292:5

overall 38:1,20
50:8 57:17 63:9
65:7,8,12 66:6
69:6,16,20 70:12
71:7,9,13 74:18
75:9 76:9 77:2
78:12 82:11
83:13 87:18 88:1
89:21 90:16 92:9
134:10 138:4
141:5 148:18
161:20 165:19
167:19 169:8
176:18

190:18,21 191:4
193:8,12 195:21
196:7 199:10
201:15,20
204:11,15
205:14 206:7,21
256:14 273:3
290:19 293:3,16
302:3 307:8,18
317:11 319:11
320:14,22 322:2
324:12 332:1
334:21 335:6
340:10,22

overestimate
320:16

**overinterpretatio
n** 210:8

overlap 66:12
316:15

overlapping 66:19
118:15

overriding 178:11

overstate 171:10

overstated 186:5

overview 15:6
44:3 153:3,10,11
156:20 321:9

overwhelmed
276:13

overwhelming
245:1 277:22
289:12 294:19
295:22 321:17

owner 240:14

———————

——— P ———

P.C 9:9

p.m 346:7

PAC 229:20

Pacific 220:22

package 111:11
179:15

PADAC 1:5 12:4,8

PAGE 12:2 13:3
14:3 15:3 16:3
17:3

pages 280:7 347:4

paid 225:9

pain 70:5 74:1
198:16 204:17

panacea 274:22

pancreatic 28:10
162:2

panel 26:6
251:9,13 265:19
292:21 301:1

paper 125:11
128:7,19 131:20
148:8 264:3
313:18,21

papers 187:8

Parad 8:12 19:6
143:4,18,19
147:15 148:6
265:17,18
269:12,17
280:18,19
311:20,21
331:2,3,6
335:3,4
337:21,22
344:17,18

parallel 29:13
159:4 164:2

parameters 48:5
62:6 69:5 275:1
310:19

paraphrasing
269:19

Pardon 130:7
143:5

parent 108:5
150:14,16

parents 121:9
150:5
218:9,12,22
263:16 275:8
277:1

participant 25:15
213:22

participants 23:11
25:16,19 32:10

participate 26:5
235:6 245:7
251:12

participated
345:22

participating 25:6
175:15 284:15

participation
26:10 81:21 86:5
152:18 329:8

particle 302:2

particular 23:19
25:10 48:19
59:21 109:18
110:21 120:11
131:19 132:6
147:13 181:19
252:6 263:17
275:10,14
284:6,10
285:7,16 291:4

particularly 52:6
54:1 81:7 119:1
120:20 130:18
136:19,22
138:17 147:7
170:5 230:17
277:21 278:20
285:4 291:22
305:6,16,17
333:20 337:14
339:6 342:4

344:14 345:5

particulate 24:16

parties 347:7,9,11

partly 334:11
338:8

Partner 9:8

partnership 233:3

pass 46:21 67:16
91:20 103:6
126:7 161:4
204:16

passed 93:13
106:10

passing 73:7

passionate 261:12

past 115:8 151:3
247:2,18 263:5
275:6 281:3
313:14,15

patent 54:11
55:4,21 56:11,22
63:18 81:2
308:22

patents 24:8

pathogenesis 82:2
238:3

pathogens
216:9,15

**pathophysiologica
l** 40:4

pathophysiology
39:1 82:15 83:1
264:8

pathway 264:14

patient 9:20 21:2
35:3 36:6,20
41:6,12 48:17
53:2 55:10 56:17
68:1 74:13 82:8
86:12 88:5,8
90:19 91:8 97:18

102:17 104:20
105:1,15
106:7,10
120:2,14,17
122:2 140:6
144:4 157:12
159:22 161:22
166:18
167:12,20 171:1
172:18 173:5
178:8 181:15
182:8,12
184:6,14,18
196:15 197:5
216:22 221:17
222:16 231:4
235:19 236:12
237:10 239:8
240:9,15 258:17
259:18 264:19
276:11 282:3
285:12 286:13
297:2 313:15
314:2
316:15,19,21
317:3 326:22
328:21,22
329:12

patients 24:14
26:15 27:7,15,21
28:12,18 29:4,15
31:3
33:6,9,11,17
34:22 36:19
37:16 38:2,10
39:16 40:10,13
41:14,16,18,22
42:4,9,13,15,19
43:1,9,11,12
46:6,20,22
47:8,9,12,16
49:7,10,12,15,17
,19,21,22 50:5
52:6,11,15
53:3,10,11 54:22
55:1
57:5,11,14,21

59:15 60:1,4
61:6
62:10,11,13,15,1
6,17,21 63:5
64:14 65:3,8
66:1
67:2,5,14,22
68:12 70:21,22
71:8,10,17
72:6,8,11,13
73:1,4,7,13,14
74:19,20 75:11
77:8,9,13,14,20
78:6 79:9,15
80:7,10 81:3
82:12 83:4,7
84:10,16 85:2,14
86:1,4,6,9,14,17
87:5,12,17 88:3
89:3,8,13,15,17,
20 90:8,12,17
91:4,6,11,20
92:2,7,11,14,15
93:20 96:11
97:9,13
98:1,7,10
99:5,11,12,22
100:1,11,14
101:13,14,16
102:19,22
103:19,20
104:3,17
105:5,8,19
106:2,16,19,22
107:3,8,21
108:2,3,15,18
110:12,15
111:6,11
112:9,12,14
113:4,16,19
114:7 116:4
118:4,9,16
119:2,3,6,9,11,2
2 121:2,8
126:16,18,19
131:7,10,11,21
132:1

133:4,13,17
135:6 139:2,15
140:4,10
144:11,13
145:16,18,22
146:1,9
147:20,21 148:2
152:13 153:17
154:3,22
157:6,14,15,21
158:1,4
159:11,14
160:14,17,19,20,
21
161:4,5,7,8,11,1
5 162:3
166:16,20,21
167:1,11
172:11,20
173:6,12 174:7
175:15
177:10,11 181:2
182:1,3,6,13
184:2
185:5,16,18
186:22 187:7,11
188:8 189:3,11
192:1,8,16
193:2,21 194:12
196:2,11,16,21,2
2 197:9,19,21
198:5,7,20
199:13,20
201:6,11,13
202:1,4,6,8,9,19,
22 203:5,12,13
204:5,8 205:8
206:11,19 207:3
216:5,6,17
217:18 219:19
220:1,2,11,14,16
221:4,11,18,20
222:1 224:4
225:1,11,22
226:2,10,12
227:3,9,11
228:12

235:5,12,14,21
236:2 237:16
238:4,6,8,13,19,
21
239:1,13,17,18
244:17
247:17,22 248:9
249:14,20
256:11
257:2,7,16
258:6,16 259:15
260:7,8 262:16
263:9 264:12,21
266:5 267:10
269:3,20 271:21
273:13,20 276:5
280:4 281:12
282:20 283:3,11
284:12,22
286:10,16,20,21
287:5,6
288:10,15,17
289:16,18,20
290:8,18
293:5,16
295:20,22
296:1,21
297:15,16,17,21
298:4,5,15 299:9
301:13
303:3,10,13
304:9,10 305:20
307:11,17
309:8,21
310:2,5,6,8
313:17 314:20
315:5 316:16,18
317:1 318:2,13
323:8,11 326:11
327:1,3 328:13
329:2,3,7 330:20
331:19 336:13
339:1 341:7
343:13 346:5

patient's 104:6
161:14

Patients 33:10
46:11 87:3 90:12
160:1,4 161:15
162:1 174:2
200:1,16

patient-years
68:10

Patrick 14:12
36:15 235:17

pattern 60:8 64:12
66:12 137:16
146:5 212:1,2

patterns 163:7
201:19

paucity 235:10

Paul 2:17 20:12
333:1

pause 269:11
331:9 336:20
341:14

payment 213:5

PC 5:13

PCP 150:19

pediatric 6:6,14
19:2,4,7
21:10,13 80:7,9
89:10,15,20 92:2
99:7 108:2,3
112:18 130:20
131:10 132:21
133:10,13 134:1
148:11 152:11
163:20 178:6,9
189:3 191:22
192:8
193:1,12,14,16
195:16 196:1
201:2,12,14
202:6,16,19,22
203:4,13 204:22
205:5 207:4
252:14,17
256:18

297:15,21
298:1,2,5,20,21
299:9 302:4
324:13 338:16
339:2,9 340:17
343:10

pediatric/
adolescent
204:5

pediatrician 19:19
108:20 140:1
292:20 295:18
321:10

pediatricians
149:14

pediatrics 6:8,17
8:13 9:13
19:1,11 31:3,18
130:18 134:14
192:6 193:4
202:18 203:6
305:1,6

peers 261:21
294:18

penalized 56:18
57:7

penalizes 55:22

penalizing 57:1

penalties 53:21
54:15 55:11

penalty 55:5,8
56:6,10,14 57:6

people 21:4 28:15
46:19 93:13
96:13,18 97:1
98:17 107:14
115:7 116:6
123:13 140:15
152:5
182:6,14,22
183:3,7,10
210:15,16 216:1
217:6 232:15,19

233:9 234:2,6,17
241:6 249:17
252:19 259:12
262:12 265:5,15
266:7,8,18
277:16 279:20
285:15 290:10
303:5 305:22
311:2 315:15
345:19,22

people's 322:21

per 33:22 41:19
148:16 151:4
243:12 270:14
304:4

perceive 260:14
315:7

perceived 297:2

percent 29:5
33:11,17 38:6,7
40:9 46:13 49:14
50:3,9,18 52:16
58:20,21 61:8,11
62:12,19
64:15,19
66:8,10,17
70:3,11,21,22
71:3 72:11,12,14
73:13,14,15,16,2
0,21 74:18,20
75:12
76:11,13,14,22
77:1,5,6,17
79:10 87:5,19,22
94:10,19
95:11,17,18
96:17 97:18
98:10
99:4,5,6,11,12,1
8,22 100:2
101:6,8,14,15
102:11,12,13,17,
19 103:1 104:4
105:3,6,7,11,13
113:18,20

114:11,14,15
115:2,5,17
119:19 131:22
132:2,11
133:12,14,20
134:9 136:5
144:19 146:18
147:4 148:3,21
149:1,2,4,15
157:7 158:9,15
160:10,11
161:1,8,15,21
167:10,11,12
168:13,18
173:3,4
177:19,20
178:16,18,19
187:7,8,10
189:22 192:2,6
193:20 194:6
197:15,16,19,20
198:7,8 199:1,12
201:6,18
202:3,5,7,14,15
203:14 204:8
206:3 208:22
210:14,16
211:11,14,19,20
222:19 223:16
224:22 226:7
231:6 233:19
247:7 249:15
250:10 259:17
269:15 273:11
279:1 281:9
282:19
283:2,7,12
293:10,11
296:11 297:14
300:21 306:2
309:11
314:4,5,13 315:1
316:17 319:8
321:13 323:15
324:20 325:1,2
327:6,9,11,14,17
328:11 329:3,7

335:8,14

percentage 192:16
196:16 309:10

percentages
319:11

perceptions
261:10

percussion 215:17

perfect 170:14
171:5

perform 41:18

performance
172:14 178:3
332:17

performed 84:18
204:1 205:20

performing
215:17

perhaps 64:6 93:5
96:21 97:7 103:7
104:12 119:2
133:20 135:19
139:22 144:20
147:17 148:12
149:20 150:13
260:6 264:1
288:12 296:6
307:3 308:10
314:17

period 29:17
47:6,22 51:5
54:21 72:17
107:8,17 108:1
109:14 145:8
157:15,17
158:10 164:7,21
167:10,13
176:19
178:17,20
191:19 193:22
197:10 198:7,21
200:12,21 201:7
231:10,11

249:18 284:16
289:21 290:9

periodically 80:4

periods 29:3,14
156:3 158:6
196:14

permanent 60:15
103:14

permission 222:1

permit 345:3

Permutt 11:5 16:7
21:7 153:6
174:21
180:7,8,12
209:22 210:9
211:3,16

Permutt's 162:17

per-protocol 158:1

persisted 145:9

persistence 39:10

persistent 89:11

person 119:17
223:6,13
265:8,12

personal 25:15
212:7 311:10

personally 281:8

person's 298:12

perspective 14:11
30:19 36:16
59:12 81:14 84:8
104:12 117:14
180:18 211:22
255:15 263:9

persuading 181:5

persuasive 183:19

pertains 284:1

pertinent 160:7
223:17

Peter 4:12 20:10

333:6 339:15 343:4

ph 303:8

pharmaceutical 25:11

pharmacies 79:17 287:14

Pharmacogenomics 20:1

pharmacovigilance 80:2

pharmacy 230:16

Pharmaxis 13:5,10,21 14:9 24:13,17 26:14 33:4 34:5 37:4 43:17 49:1 59:6 67:19 220:12 235:7 240:4 257:18 331:17

PharmD 2:4 12:7

pharyngeal 201:10

pharyngolaryngeal 70:5 74:1

pharynolaryngeal 198:15

phase 29:11 33:13 36:11 44:4,21 45:6,10,12 46:1,3,7 47:12,16 50:5 62:20 67:21 68:4,7 72:9 84:14,18 86:7,14 97:8,22 98:6,13 99:9 100:10,14,16 117:5 137:12,18 145:19 146:2,10 155:11,13 156:22 158:21 159:1 163:3

191:20 198:18 201:7 209:2 221:20 309:7 312:1,9,17

PhD 2:12 4:6 7:5 10:5 11:5 13:8,13 14:7 16:7

phenotype 286:13

phone 315:11

phones 18:6

physical 218:13 246:22

physician 21:13 121:7 303:11

physicians 43:1 74:6 79:1 88:14 92:11 276:6 277:19 288:19 340:2

physiotherapy 110:21 154:4

pick 102:10 107:21

picture 131:5 136:4

piece 98:5 148:13

piggyback 274:15

piggybacking 275:22

pin 307:14

pinpoint 31:11

pipes 116:7

pivotal 47:19 51:8 65:6 85:9,17 86:3 87:20 121:20 132:11 138:14 324:17

placebo 29:17 45:1 87:21 107:12

132:10

placed 35:12

places 342:10

plagued 273:11

plan 51:1 142:10 150:9 162:9 166:3 235:19

planned 48:12 93:18 165:3

plateaus 288:3

plausibility 129:2

plausible 54:14 56:20

play 204:16 262:13 263:11 301:15

played 181:4

player 244:7

playing 223:14

please 18:3,5 22:16 103:10 105:6 113:9 210:13 211:5 214:2,9 228:16 229:2 232:22 234:20 240:1 249:4,9 250:2 251:5 267:4 296:7 300:17 308:17 309:6 313:11 321:2 322:3 323:5 324:19 327:12 329:22

plot 55:14 57:18 66:5 119:9 127:18 135:4 172:10,17 177:6,8 180:2 250:17 320:10

plots 142:8

192:5,8 273:13

plugged 302:16

plugs 302:21

plus 244:22 259:17

pockets 311:4

podium 32:1 94:21 128:22 153:6 251:20

point 45:9 47:5 51:11 56:4,7,12,15,19 57:1,3 59:5,7 83:22 100:5 104:20 107:9,10 114:10,21 115:22 121:20 129:1,2,12 130:5,8 140:9 171:12,21 194:4 195:4 206:1 211:4,14 212:3 233:8 242:8 248:7 249:21 251:1 256:18 259:2 269:1 270:4,16,18 278:12 285:17 289:14 292:2 297:6,19,20 298:7,22 299:2 309:2,20 311:13 316:12 321:4 323:4

pointed 64:7 259:12 297:8

point-of-care 79:18

points 59:9 94:9 126:11 184:8 251:19 256:2

Pokey 242:19

pool 326:5

pooled 44:7 65:17

66:5 119:11 138:9 147:2 192:5 321:3,5 325:7 326:6

poor 39:7 43:10 230:20 236:21,22 237:1,2,4 322:19 334:2

poorly 206:18 236:22 237:2

population 30:21 31:20 43:20 48:18 49:1,2,4,6 50:17 52:17 53:14 55:7,16 56:5 59:7,19 61:7,18 62:9 63:7 65:12 68:5 69:22 71:14 76:9 77:2 89:10 93:18 98:12 112:18 116:2,4 124:3,21 127:4 132:1 133:10,11 134:22 135:17 136:14 141:5 147:12 157:15 160:18 161:7,9 165:14 166:9 167:2,3,7 168:1 169:4 174:1 175:12 189:10,21 191:22 192:2,9 193:6,10,16 194:17,20 195:21 197:10 198:6 199:15 201:14,20 202:6 204:22 205:12 207:4,6 237:22 252:17 255:19,20 261:11 268:3 274:5,6,11

276:11 280:1 282:22 283:2,10,14 285:19 286:9 290:5 292:16 298:1,20,21 312:22 314:3 316:17,21 317:3 319:7 320:20,22 323:16 324:14 326:10 328:5 332:2 334:15 335:22 338:19 344:8 345:5

populations 143:6 161:22 284:3 316:19

portability 42:1 91:10

portable 36:4

portion 188:14 189:18 248:15,21 251:10 302:17

Portland 3:11 20:6

portray 187:17

posed 207:11

position 241:22

positive 61:9 64:11 98:18 99:1 114:22 154:4 157:13 160:21 179:4 186:2 190:5 191:7 205:18,21 243:21 246:8 253:18 276:15 290:16 334:4 337:16

positively 344:21

possibilities 40:16

possibility 52:5 66:1 186:1

292:17 342:17

possible 61:4 186:15 191:16 311:19 312:4

possibly 72:16 140:9 264:8

post 51:10 52:8 61:8 65:3 80:6 81:11 113:3 139:7 169:13 289:1

post-baseline 166:13,16,18,21 169:6

post-dose 61:17 64:21

posted 316:13

post-hoc 48:10 138:12,14 139:10 141:9 156:9,10 172:8 325:9

post-marketing 288:22 332:18 342:9

post-randomization 273:4

potential 23:17,20 24:1 31:16 51:18 55:17 73:2 169:10 219:17 226:19 243:16 293:21 338:12

potentially 119:21 224:18 243:17 312:4 317:4

potentiate 40:6

powder 1:7 24:11 33:5 35:11,14 43:18 91:9 152:22 153:1

154:10,11 155:3 226:18 227:9 232:13 245:8 258:4 290:20 301:9 302:1 325:17 332:16

powdered 256:9,14,16,22 257:6,14

power 58:18,19,21 245:2 326:18 327:5,8,15

powered 58:6 65:13 209:9 324:7

practice 18:20 19:2,3 20:20 84:5 90:4 105:4,17 106:13 120:13 122:16 140:12

practiced 277:12

practices 275:18

practitioner 276:9

pre 100:11 162:7 163:10 166:2 168:7 172:2,3 176:15 180:8

pre-bronchodilator 98:9,11

precautions 78:22 267:21

precise 181:11

preclude 32:22 213:13

predefined 290:9

predict 104:6,10 108:11 109:5 121:7 122:10,21 127:11

predicted 33:11

46:13 50:18 66:8,10,17 136:5 144:19 146:18 147:5 148:3 149:4,15 157:8 160:10 161:21 201:18 203:15 208:22 211:14,20 222:19 231:6 306:2 323:15

predicting 99:16 119:19

predictive 148:21

predictors 165:10,11

predominantly 303:17

pre-dose 115:1

pre-dosed 46:22 103:12

pre-existing 59:22

prefer 258:13

preferably 141:3

preferred 70:12 197:11

preliminary 280:11

prelude 260:17

premature 156:11 216:21

prematurely 53:2 117:18

pre-medicate 139:16,18

pre-NDA 141:7 156:7

preparation 34:6,9

preparations

301:10

prepared 211:17 306:20

pre-planned 55:16 62:2

prescribe 117:1 227:14 276:9 340:2

prescribed 226:7 253:7 254:21 255:1 266:1 275:9

prescribing 78:22

presence 163:12,16 248:13

present 18:5 36:11 43:18 44:5,13 65:16 67:17 76:6 163:13 172:4 174:8

presentation 32:9,18,21 36:8 37:1 43:14 68:16 70:17 81:12 92:19 153:2 156:18 158:22 159:7 160:16 162:13,15 163:17 174:22 179:16,17 188:13,15,21 194:6 201:3 207:15 212:20 274:21 275:12 278:5 279:15 327:10

presentations 13:4 14:4 15:4 26:18 32:4 33:1 151:8,13 152:2,7 153:15 189:17 345:20

PRESENTATIO

NS(cont 16:5

presented 30:17 63:15 81:16 84:1 88:13 94:6 96:9 125:3 144:18 156:8 170:12 175:7 183:21 188:17 195:17 205:17 251:15 275:5 331:17 333:19 339:5 345:8

presenters 14:17 16:16 32:11 93:3 208:4

presenting 76:8

presents 66:5 172:19 201:4

preservation 202:22

preserving 170:21

president 33:3

pre-specified 48:21 162:7 165:7 170:7,11 171:18,22 176:17 179:8 180:21 181:9 183:18

pre-specify 209:11

press 18:8 35:18 329:22 330:2

pressure 154:5

presumably 61:13 96:18 98:16 101:18 124:8 264:8

pre-treat 100:6

pre-treated 97:9 100:15,17 199:21

pre-treatment

100:18 101:9

pretty 119:14 208:14 210:6 277:14 281:7 282:19 304:18 315:4

prevent 82:13 306:4

preventing 83:2

prevents 55:14

previous 64:8 77:21 189:16 200:1 272:3 283:9 317:7 332:8 341:11 343:20

previously 30:22 61:3 87:20 161:18 169:3 191:15 195:9 293:5 341:21 343:17

primaries 325:6

primarily 63:17 180:13 254:9 332:17 339:9 343:10

primary 24:9 29:4,15 44:17 47:21 48:1,13,20 49:1,5 50:2,21 52:1,17 53:14,17 54:19 55:14,16,20 58:9 60:22 61:20 62:1 64:7 144:17 146:19 155:14 156:5 159:17 162:5,22 163:11,16 164:19 165:1,9,21 170:8,11 171:18 172:5,9

174:12,19 175:4 177:3 180:2,10,21 181:9 182:20 184:1,20 185:9,22 186:5 189:8 190:4 192:20 193:22 207:12 208:6,7,11 272:7 291:1,16 324:22 326:8 327:7

principal 220:10

principally 332:7 342:1

prior 47:1 53:5,10 62:17 87:8 95:12 113:5 146:3 170:22 198:1 199:21 200:4 204:8 215:8 344:19

priority 271:2

private 18:19 20:20

probability 122:9

probably 37:10 102:5 108:13 112:9 117:10,12 123:10 131:1,4 144:16 150:17 186:5 218:10 251:22 266:5,6,13 267:8 268:17,22 279:12,13 292:6 310:10 319:9

problem 185:1 223:18 225:10,21 260:1 273:19 283:17 306:7 338:19

problematic 30:2 124:4 158:4

178:14 195:1 230:14

problems 28:11 115:16 180:16 293:15 296:19 311:11

procedure 160:22 166:5 337:2

procedures 42:5

proceed 26:1 32:3 69:2

proceeding 348:3,4,7

proceedings 22:13

process 32:6 35:15 36:2 87:1 95:5 212:16 213:15 217:10,21 240:8 271:17 280:17

produce 35:9 262:18

produced 54:3 102:17

product 25:3 27:12 41:9 68:20 153:9 154:14 155:20 172:16 180:14 181:5 196:10 213:3 253:4 255:3,6 264:15 284:1,10

productive 22:6 245:16 246:21

products 10:8 12:13 21:17 25:14 41:5,7 152:11 217:15

professional 37:8

professionals 80:1

professor 2:18 3:8 4:13 5:8 6:8,17 7:6,13 8:6,13

9:6,13 13:14 14:13 18:18 19:1,11,14,17 20:10,12,18,21 43:16 224:10 296:7

profile 67:20 68:15 71:9 80:21 83:6 92:9 153:9 189:5 193:15 195:22 256:14 257:6 275:1,20 290:20 291:14 319:20 336:12 339:21 340:22

profound 237:18

program 4:8 15:6 26:20 28:21 29:22 43:19 44:3,20,21 45:6,10 68:11 74:16 80:9,11 97:18 98:6 100:11 115:12 139:8 153:4,11 156:19,21 157:2,4 162:17 199:11 205:14 224:13 229:6 235:4,7 244:12 252:6 326:15

programming 240:6

programs 2:7 46:4

progress 160:1 246:7

progresses 38:19 245:4

progression 233:6,15

progressive 38:9 41:7 82:4 216:20 293:9

progressiveness 293:12

prohibited 161:19

Project 229:19

projects 239:11,15

prolongation 297:11

prominently 167:18

promote 34:13

promoting 237:16

pronounced 202:18 294:5,14,18

propagate 125:16 128:10 129:10

propagating 125:13 129:8,13

propagation 126:2 129:13

proper 236:9 275:20 323:7

properly 96:10,15

properties 159:20 259:14

proportion 101:13 102:1 113:16 138:18 172:19,21,22 173:5,12,21 174:6,15 177:13,18 192:19 249:14

proportionately 300:1

proposal 156:9

propose 33:16 79:4 163:13 281:14

proposed 24:12,13

27:8 29:7
33:8,14 45:13
73:10 150:9
153:9 154:12,20
155:1,19,20
159:2 164:22
192:1 253:7
265:21 266:2
267:14 269:2

proposing 78:21
144:3

proprietary 33:19
34:6

prospectively
48:12 142:10

protein 28:7 40:7

protocol 162:6,11
165:2

prove 90:10

proven 40:9
259:11

proves 271:22

provide 35:7 36:16
37:6 44:2 45:12
56:2 58:3 59:11
79:2,18,20
106:18 153:7
173:17 189:15
194:2 195:12
237:18 243:20
252:15 257:13
279:17 311:16
341:4

provided 23:10
29:1 158:11
174:12 175:11
213:16 293:4
331:19

provider 150:10
279:17

provides 60:12
65:7 83:22
146:13 166:7

171:11 173:20
250:7,8

providing 57:16
153:3 166:16,18
188:18 189:4
240:5

provisos 335:5

provocation 31:1

provoke 46:19

Pseudomonas
162:4 222:6
223:3,16 314:20

public 3:15 6:10
7:8 8:8 16:18
20:17 23:11 25:2
26:3,4,5 32:5
212:13,15,18,22
213:15,20
214:6,10
248:14,19
251:11 261:8
262:9,10 263:9
270:7 274:17
275:2,11,19
276:20 277:6
278:21 279:19
285:14 291:11
294:7,22 311:3,5
329:11 336:8
347:1,18

publication 91:21
117:20 131:15

publications 41:18
131:14

published 54:5
61:3 78:14 84:20

puffs 101:5,9

pulmonary 3:10
4:14 7:14 10:7
12:12 14:13
19:15 20:5,11
21:13,14,16
24:15 26:15 27:8

28:9 33:10 74:5
77:20 81:22
82:10 85:5,8
87:15 88:10
91:15 92:6
105:22 132:12
134:12
152:10,16
154:22 175:8,11
182:10,15,16
190:16,18,22
191:4,10 195:15
197:14 206:17
217:3 220:15
221:5,7 222:12
231:9 256:10
257:1,17 258:6
267:10 269:22
296:15 325:12
328:1 330:19
341:8 342:16

Pulmonary-
Allergy 1:4 2:9
3:3 4:3 5:3
18:12,13 20:8
22:21 26:10
346:8

pulmonologist 6:6
19:7 21:10
152:11 235:3

pulmonology 6:14
19:2,4

pulmozyme 28:1
238:9 316:20
317:8

puncture 35:19

punitive 170:17

pure 146:21
258:21

purely 137:8
291:21

purest 261:2

purple 167:14

purports 253:5

purpose 123:2
268:4

purposes 24:4
62:3 158:19
194:18

pursue 239:3,15
246:10

pushed 230:12

puts 242:12

p-value 272:21

—————————

Q

—————————

qualify 102:20
260:12

Qualitative 69:15

quality 175:9
176:13,14 177:1
191:2,11 216:3
217:1 231:2
235:6 238:21
239:10,15
242:4,5 322:20
343:21

quantified 165:1

quantifies 229:21

quantify 88:12
169:7 180:9
237:6

quantity 322:21

quarter 82:20

question 86:19
93:4 94:1 96:7
102:9 103:6
104:5 106:5
107:6 108:19
109:3 111:18
112:3,8 116:20
117:3,5,13 122:8
123:4 134:13
139:13,17
140:21 143:5,21

144:8,9 145:4
147:14 148:8
149:16 150:3
151:22 152:1
181:18 182:20
193:10 207:12
208:5 209:8
250:1,11 252:4,9
256:6,8,13,15
257:5 258:3,13
259:9 261:17
266:11 268:20
269:1,11
293:3,18 299:17
300:7 305:8
306:13 314:12
316:3 319:18
322:16 330:16
331:1 335:5
336:12 338:1
341:3,4 345:6,8

questionable
30:10

questioned 291:1

questionnaire
80:3 176:15

questionnaires
150:10

questions 14:17
16:16 36:18,20
83:4,10 92:22
93:1,3 116:21
124:2 130:16,17
134:15 143:20
151:8,14,19
207:10,19,20
208:3 209:18
248:22
251:2,6,19
256:2,7,19 258:1
265:22 280:16
328:18 329:15
330:14 331:3
341:11
343:5,7,20

345:17

quick 234:6 302:7

quickly 97:2,15

quite 21:22 59:2
63:22 64:6
115:16 121:3,10
145:11 146:5
246:11 279:16
280:2,8 288:10
294:9 301:14
302:16
308:19,21
310:10 312:22
314:16 327:22
336:16

quote 223:6

--- R ---

raise 119:1 263:14
342:17

raised 118:16
270:19

raises 170:5

raising 193:10

ran 243:6

random 51:17
52:3 125:19,21
126:3
127:11,19,22
128:2
129:19,20,21
130:1,11
169:15,21
170:1,19 178:4

randomization
47:5 125:1 137:4
164:2,16 194:18
204:9

randomize 290:11

randomized 46:9
47:8 49:11,15
62:13 157:18

158:6 159:4
160:2 164:2
165:15 186:22
221:18 230:7
297:18 298:2

randomly 185:6

range 30:17
31:10,13 38:14
46:13 54:14 68:1
74:10 87:22 88:7
103:1 144:10
194:5 195:4
202:20 206:1
279:1 281:14
282:19
286:15,16 317:3
334:9 345:5

ranges 250:7
316:15 317:4

ranging 45:2,14
87:12 157:5
161:3 300:6

ranking 162:8

rapid 145:9

rapidly 145:8

rare 72:22 131:17
293:4

rate 44:16 50:8
52:19 61:9,12,13
63:1 64:3,20
69:20 82:13
85:15 86:1
88:1,6 104:2
109:15 110:1,3,5
111:8,13 132:11
162:2,3 165:20
170:4 175:10,22
176:8,9 197:18
198:2,19 199:1
200:22 201:5
202:3 203:5,6,14
217:2 259:17
297:14 325:16

326:22 340:8

rates 59:2,15
63:16 78:13,14
87:21 167:14,17
169:16
200:6,17,21
205:9,10 207:6
324:16 334:3

rather 31:11 44:10
55:7 74:2 111:14
134:2,3 150:17
184:9 186:7
187:22 190:13
228:11 250:22
263:13 274:21
275:4 288:16
307:3 309:19

ratio 46:10 61:10
121:4 344:20
345:4

rationale 101:21
103:9 104:13
332:15

Ratjen 13:13 36:9
37:2,3 43:16
60:4 90:13
108:20 109:2
140:1
148:12,14,22
292:20 293:1
295:5 296:7,14
301:4 302:3,12
306:21 307:5
308:4,7 316:1
321:8,12 323:1

Ratjen's 121:18
202:18 308:17

reach 57:3 107:8
114:10 195:11
206:14

reached 51:12
94:14 98:21
245:13
299:11,22 300:1

333:9

reaction 96:22

reactions 201:5

reactive 106:2
116:8

reactivity 102:12
105:20

reading 100:7

ready 90:21 331:7

real 58:4 61:12
66:21 90:18
146:16 178:3
223:18 226:3,9
230:8 232:17
235:20,22 286:8
306:7 309:18
331:20 342:9
345:2

realistic 164:11
175:20 186:8

reality 59:20
230:10

realize 247:19

realized 280:15

real-life 227:1,6

really 67:12 93:20
102:22 103:1
106:4 107:7
110:15 112:13
118:8 119:14
120:12,13
121:16 124:22
125:4 136:20
137:13 150:12
209:16 218:9
221:6 223:21
225:15,17
226:15
228:10,16
230:18 243:16
259:8 264:10
269:5,18 270:1,4

271:5 274:3,12
281:10 283:19
284:21 292:12
296:9 299:16
302:10 312:17
317:10 321:6
322:2 339:2
341:10 345:4

reason 32:10
49:11 50:11
96:14 101:16
103:8 111:12
137:13 169:18
196:22 197:4,7
212:21 224:15
255:4 282:13
299:4 310:15
330:13 338:8
339:16

reasonable 120:16
121:8 127:1,3
155:16 156:1
182:5 196:8
203:19 237:19
249:21

reasonably 50:16
63:6 108:16
118:16 187:19
338:3 344:13

reasons 46:17 63:2
101:21 109:13
112:3,15 157:14
167:19 302:9
333:7 339:14
341:21
343:5,7,17

reassessed 47:13

reassurance 56:2
65:7

reassure 53:13
195:13 206:15

reassuring 295:19

recall 86:4 103:10
114:14 133:15

156:21 199:12
323:11 324:18

receive 146:10
160:3 161:5
164:5 165:15
200:20 246:12
309:15

received 47:8,9,17
114:12
157:16,22
159:13,16
198:11,20
200:16 204:5,6

receiving 49:16
62:14 161:16
196:16 199:8
205:11

recent 33:12 50:9
84:20

recently 19:12
28:16 91:17
153:16 314:21

recess 212:11
328:16

recessive 28:4
37:11

recognition 74:6

recognize 51:17
55:17 77:9 132:9
291:21 296:12
306:8

recognized 22:5
27:2,4 33:21
58:8 60:4 68:19
76:3 78:20 80:22
109:15 214:2

recognizing 59:10
86:12 323:4

recollect 150:18

recommend 85:6
88:17 110:18
128:8 257:4

recommendation
91:18 231:20,21
243:21 268:6
270:9 277:2

recommendations
54:16 88:14
110:11 132:13
133:1 165:18
196:10 277:1,5

recommended
40:20 41:5 42:4
54:11 79:10 85:4
91:19 253:7
255:1 266:2

recommending
121:21

recommends 73:3

record 22:5 25:18
330:8,10,12
347:6

recorded 72:7
133:18 347:4

recordings 348:5

recovered 97:19

recruit 284:3

recruiting 284:22

recurrent 303:19

red 142:1,12 167:2
172:22 173:15
192:17,21
220:20 231:8

reduce 40:15
217:2 220:2
224:3 325:14

reduced 56:16
61:7 64:15,18
77:16 287:4
347:5

reduces 92:5

reducing 66:12
83:2 134:12

reduction 43:3
61:9,13,14 64:19
85:8,19 288:4
324:13,21
325:5,16
327:9,14,17
328:11

reductions 60:21
327:11 328:10

refer 152:22

reference 165:21
179:20 187:6
192:15 229:17

referenced 231:18

referred 48:22
154:10 159:8
163:14 172:9
231:15

referring 289:2

refill 226:1 230:16

reflect 59:19
190:21

reflected 63:10

reflecting 50:20
147:20

reflective 168:4
209:3

refrain 22:14,17

regard 31:18
145:4 199:15
206:18 207:4
254:17 267:7,18
290:1 297:6,20
316:20

regarding 56:2
67:11 79:2
163:19 164:12
165:18 168:2
170:6 175:2
178:6 179:9,13
193:4 264:5
265:20 268:15

278:3 334:1
339:21 342:18

regardless 40:14
68:2 74:22
115:22 175:21
181:2 204:14

regards 130:16

regimen 83:8
111:2 154:4
159:2

region 138:1,2,5
164:3 320:18

regional 250:21

regions 138:10

registration
155:19 316:22

registries 88:8

registry 80:11,15
131:15 231:4
289:15
292:9,14,17
303:21 306:9
313:15
328:19,22
329:13

regular 23:4,16
46:15

regulated 25:8

regulations 23:6
252:21 270:14

regulator 28:6

regulatory 13:9
33:3 155:5
194:18 196:9
252:4,19 253:10
255:15 272:6
332:7 333:3
340:16

regulatory-ese
253:9

rehydration 40:7

reimbursed 37:5

reinforce 184:9

reinstitute 88:21

reiterate 229:11

rejection 275:16

relate 249:7
250:17 262:7

related 23:21
24:17 27:11 70:8
71:22 117:13
154:14 166:20
175:6 179:5
206:5,21 211:10
243:9,13 249:5,6
250:13,14
294:13 302:4
305:5 316:2
328:4 338:8
347:8

relates 119:2
120:13 135:10
250:1 287:3
303:11

relation 110:22
275:4

relationship 213:2
288:13

relationships
25:20
32:12,19,21
213:10,12
214:21

relative 43:5 71:13
75:6 147:11
174:18 196:1
235:10 325:18
347:10

relatively 147:10
149:2 304:22

relax 242:20

release 35:20
96:12

relevance 31:13

relevant 48:4
78:21 86:20
117:13 183:12
327:18,21
328:12

reliable 253:20

relied 170:18

relieve 82:18

religiously 245:2

rely 247:22

relying 314:1

remain 38:5 46:15
70:9 86:15 190:3
288:12 323:17

remainder 159:7

remained 157:14

remaining 36:2
167:1 274:8

remains 28:14
38:2 58:1

remarkable
288:10

remarkably 65:6
138:10
308:19,21

remarks 12:10
26:2,7 185:12

remember 55:21
103:15 116:19
197:21 272:11
273:13 288:13
292:15 296:13
305:16 319:7

remembering 51:6

remind 18:5 25:12
26:3 186:21
212:8 287:10

reminded 22:16
277:16

reminder 22:4

reminds 230:4

remote 215:4

removed 204:8
215:9

removing 35:16

repeat 91:2 112:20
299:16

repeated 36:2
48:14 165:10
181:10

repeating 292:11

replacing 287:15

replicate 253:12

report 54:4 75:17
150:18 175:16
298:14 313:22
323:13 326:19

reported 1:19
24:19 69:19
72:22 73:12,15
74:13,17,19
75:4,15,19
76:4,7,16,17
77:4 78:10,14
87:18,21 88:7
132:11 133:16
166:21 197:15
200:5 204:2
298:11 305:12
348:3

Reporter 348:3

Reporter's 348:5

Reporting 1:20

reports 200:13
314:1

represent 25:9
53:1 81:5 178:2
184:4,13

representative
3:14 5:7 9:20

23:2 25:5,7
43:19 50:16 63:7
195:14 206:16
286:18

represented 152:3
172:22 184:16
198:17 253:5

representing 21:3
62:12

represents 49:13
57:18 68:14
184:19 207:13
319:9

reproduce 283:8

reproductive
28:11

request 26:6 54:2
91:11 251:12

requested 73:9

require 48:16
156:16 169:22
208:15,17
221:8,9 236:9
324:8

required 30:7 61:4
156:6 164:14
172:18 208:14
314:20

requirement 48:7
62:1

requirements
208:20 264:16
272:7 340:16

requires 125:1
221:7

requiring 36:5
56:19 64:15
169:14

rescue 61:12 175:8
176:9 191:10

research 1:2 2:13
20:1,2 54:3

214:15,17

resistant 233:16
247:15

resolved 71:4
74:22 78:6 88:20

resource 251:5

respect 25:4
83:9,20 91:17
214:1

respectfully
277:11

respectively 76:14

respiratory 8:18
13:14 31:17
69:13 82:5 91:22
153:21 176:14
198:1 216:6
217:17 236:8

respond 63:20
104:10 127:8
177:8 249:17
285:15
286:13,21,22
288:17 289:13
294:3 319:13

responded 122:2

responder 58:16
59:10,13 63:16
163:15 172:19
173:1 174:6,20
177:6 192:8
286:9

responders
122:17,18 123:5
172:21 177:13
210:2,8,12,20
264:10 286:21
288:12,18

responder-type
285:18

responds 241:20

response 41:13

58:11,12,13
59:1,9,14 66:2
85:13 104:6
120:19
121:6,7,10,11
123:16 125:2
158:17 172:10
179:3 180:1
210:15,17
288:11,13
291:3,5 322:14
325:21 335:9,15
336:18 341:12

responses 125:16
140:20
264:9,13,20

responsibility
263:13

responsible
162:21

responsiveness
106:1

rest 184:12 308:22

restricted 269:13

restrictions 269:6

result 37:22 50:21
53:18 58:17
61:16 83:18
89:14 110:8
163:17 167:8
168:7,14 171:10
175:13 177:7
186:2 190:5,7,15
205:21 272:19
307:4

resulted 87:4

resulting 37:11
60:10 168:5
170:7

results 30:8
39:5,11 45:13,14
47:19 51:18
55:12 61:19

63:11 68:2
84:7,8 85:21
107:4 125:6
126:6 165:13
170:13 176:8
180:19 187:15
188:2,4,21
190:2,3 193:4
195:19 254:21
255:2 273:3
274:3 289:11
331:17 342:20

retention 39:9,14

retesting 145:7

retired 19:12

retrospective
87:17 131:20
314:1

return 92:19 153:6
184:19 255:8

returned 215:5

reverse 117:11
310:8

reversed 113:4
273:22

reversibility 104:7
285:21

reversible
97:15,16 105:15
144:22

revert 57:11,22

review 15:11
16:13 33:4,15
36:8 44:13 71:21
131:20 152:21
153:5,7 156:13
159:2 162:19,22
170:18
188:10,20
193:17 196:6
201:12 231:17
261:9 334:19

reviewed 117:7
180:13 325:12

reviewer 10:17
11:12 15:8,13
21:5,10

reviewing 278:19
280:7 338:9

reviews 271:3

rhDNase 45:4 48:9
50:19 62:6 63:9
65:12 66:7 84:12
85:3,17 117:8
118:5 161:17
164:3 314:8,13
324:18

Rheumatology
10:8 12:12 21:17
152:10

rib 217:9

rich 151:5

Richard 8:12 19:6
337:22 344:18

rid 216:9

right-hand 59:14
135:7,12 136:8

rightly 121:3
184:21

rise 201:1

risen 317:12

risk 33:18 42:6
61:6 64:13 67:8
69:11 73:3,6,10
74:14
77:13,15,21
78:16,20 79:12
80:5,8 87:8
89:7,18 90:1
92:10 108:15
134:10 154:18
157:9 195:22
201:2,16 282:14
286:6

292:3,5,10,13,19
,22 293:18,20
294:22 296:9,17
299:9,19 309:3
320:6 337:13
338:4 340:1
345:3

risk/benefit 14:11
16:13 36:16
81:13 89:18
153:8 188:11
189:5 193:15
255:9 257:12
294:7,17 320:2
344:20 345:4

risks 79:1 206:18
255:12 335:18
339:9

road 122:16
340:18

Robert 6:5

robust 54:15 64:4
84:21 150:19
209:6

robustness 54:11
56:21 125:7

Rock 218:4

Rod 125:12

Rodney 3:13 20:15
340:6

role 25:8 181:4
204:16 217:20
287:12 345:7

rolled 198:21

Ron 33:2

Ronald 13:8

Ronnie 240:3

room 1:13 222:2
252:19 266:7
279:3 330:11

Roster 2:1 3:1 4:1

5:1 6:1 7:1 8:1
9:1 10:1 11:1

rotated 220:19

roughly 206:2
314:14

route 27:4

routine 36:5
243:3,4

routinely 46:22
60:5 84:9
100:11,15

Royal 104:16

royalties 24:9

RS-23 249:9

RTT 47:7

rule 127:19 151:18
186:1 265:13

run 55:12 107:22
117:17
219:11,20
224:12 245:19
247:8

rung 279:2

runner 244:7

running 223:22
245:18

runs 64:5

rural 276:20
277:12

rustle 148:8

———————
S
———————

Sacramento
215:17

SAEs 73:17
299:3,4

safe 27:4 33:21
68:20 80:22
90:10 237:9
238:18 254:20

255:3,6 261:19 262:11 263:15 268:9 338:3

safety 14:6 16:13 26:13 31:1,15,16,20 36:14 46:9 67:17,20 68:5,11,13,15,16,21 69:1 74:2 76:9 80:19,20 81:1,9 83:6 86:19 92:9 104:19 105:7,11 106:17 115:14 116:14 130:16 136:19 153:7 155:18 160:16 161:10 188:11,20,21 189:2 193:14 196:6,9,12,13 197:10 198:6 199:5,6,9 201:12,14,15,20 202:8 204:7 205:12 207:14 252:10,12,13,16 254:17 255:7,19 256:14,16 257:5,6,9,10,13 261:22 266:9 268:13 290:19 304:16,19 305:9 306:13,16,18 310:15,20 316:17 319:19 322:9,17 326:4 336:12,15 339:5,17,21 341:4 342:6 343:10,22

saline 27:19 40:19 46:17,18 85:3,7,18 154:7 160:15 161:19

222:10 223:8 225:18,19 226:6,8,17,22 227:5,11 231:14,20 232:3,11 237:12 238:9 239:5,19 246:6,16 247:6 282:9 287:12 313:3 316:2,5 325:9

salty 226:13

sample 326:20

SAP 165:7,8,14 166:4 168:7 176:19 326:19

SAPs 165:4

save 219:18

saved 143:19

saw 64:18 84:19 110:3,4,5 141:15 192:4 194:5 264:1 289:11 300:6 307:19 308:22 312:20 314:2 317:12 324:12

Sawicki 229:19,20

scant 87:13 131:17 133:2 315:10

ScD 8:5

scenario 97:5

Schaller 218:1,2

schedule 243:4

schedules 239:20

schematic 47:3

schematically 184:5

school 2:20 4:15 5:12 7:8 8:8,14 9:7,14 18:19

19:9 20:14 218:11 219:1 221:12 236:2 320:3

science 3:9 20:6 79:20 217:14

Sciences 11:9 15:16 16:10

scientist 2:13 20:1 264:19

score 182:11 184:18 185:1

scores 184:2 185:5 191:12

screen 93:15 98:7 106:2 330:6,10

screened 24:1 49:10,12,14 62:11,12 72:9 96:10 98:8,9 101:14 116:5 199:12 204:8

screening 37:18 47:4 72:5 87:1,2 96:14,15 140:21 141:22 142:4,15 143:2 159:22 160:20 198:1 250:13

se 304:4

seats 18:4

second 30:14 103:18 104:5 109:17,21 110:3 117:4 134:13 189:18 197:16 202:2 215:13 238:19 256:13 259:12 272:9 298:7 305:8 334:4,13 336:11

secondary 48:4 60:7 61:21 156:5

162:5,7,8,10 163:18 165:1 166:1,6 175:1 179:10,14,18 191:5,9 195:8,10,12 206:13 208:9 209:6,12 284:9 323:20 325:6

secondly 44:16 169:12 286:19 326:5 332:18

seconds 35:22 214:7 243:8 276:16

secret 330:6

secretions 82:17 154:2

section 23:10,15 24:4 78:22 115:18

sectional 57:19

seeing 68:2 106:12 136:15 141:21 187:21 324:2 328:3

seem 56:20 58:4 59:16 125:3 134:2,3 136:11 138:16 170:16 179:13 301:17 305:12 308:14

seemed 110:2 149:6 338:22

seems 64:2 66:2 77:11 92:10 103:4 108:14 110:7 124:5 126:18,22 251:22 306:10 321:20 344:2

seen 50:9 59:6 63:19 67:13 70:7

82:8 90:5,17
92:7 106:13
116:22 120:14
139:8 149:8
158:12 183:20
186:7 188:7
189:16 191:17
193:5,12 194:2
199:8 200:15
201:19 205:17
218:17 220:20
275:6 280:12
296:16 298:18
301:1 307:3
316:14 325:17

selcting 273:4

select 138:14
208:19

selected 158:20
175:1,7 194:17
208:11,21

Selecting 273:1

selection 29:2,6,8
129:3

selects 106:15

self 230:10

self-management
232:18

send 150:10

sending 104:22

senior 2:13 19:22
264:3

sense 110:7 262:17
263:10 266:4,11
279:22 280:1

sensitive 46:20
261:10

sensitivity
30:6,11,16 31:10
44:14 49:4
53:15,20
54:12,17

55:13,14,19 58:2
64:2,5 115:21
116:1,12 119:18
123:17 126:21
129:4
141:6,12,14
142:21 143:1
163:13 170:9,15
171:3 180:9
181:5 184:6,16
185:21
189:15,19 190:9
194:1,4 195:3
205:20 206:2
209:22 249:9,16
250:20 252:8
278:11 342:22

sent 280:8

separate 206:5

separated 258:13

separately 75:19
76:8 136:7

separating
133:7,10

separation 173:10
192:22 193:8
211:5,21 260:4

sequelae 153:18

sequence 158:5

sequential 94:7

sequentially 159:3

series 51:21

serious 28:14
70:10,13,14
71:15 73:8 78:4
153:13 170:6
188:22 196:17
197:8,13 200:6
202:9 203:7
204:12 255:10
261:16,20 262:4
297:9,10 307:21

seriously 292:1
293:2 303:9

serum 301:18

servant 240:4

service 23:19

session 16:18
24:21 212:18
235:20

setting 88:17
133:1 157:12
159:22 171:13
302:18 335:9

setup 42:2 232:5

seven 41:19 62:16
72:8 107:12
156:21 157:7
166:17
187:10,12
234:20 283:12

several 71:20
88:13 170:18
173:19 215:1
218:14 248:22
254:5 294:12
323:14

severe 27:15 72:18
73:10,15,22 78:4
89:7,9 140:13,15
148:5 154:19
157:9 200:9
201:13,17
202:1,4 204:13
205:8 293:6,13
305:19 317:1,22

severely 38:5

severity 40:14
50:18 66:7,11,13
74:13 75:3,5,10
77:18

share 44:6 60:6
135:18 138:3
141:1,15 152:17
186:13 215:21

244:5 271:16

shared 126:22
321:4 324:16

sharing 145:20
270:12 346:5

Sharpe 240:2,3
244:2

shift 311:9

shifting 310:14

shopping 145:11

short 101:2 150:11
156:3 234:9

shorter 91:10

shortest 246:4

shortly 126:10

showed 55:8 69:15
100:16 104:1
119:5 124:17
126:13 135:3
162:2 173:3
186:12 191:7
236:21 249:5
254:11,22
265:20 267:8
273:16 287:2
288:12 321:21
323:2

showing 44:14
55:15 90:8
141:19 147:2,4
149:3 165:13
227:17 249:6,7
253:20 272:14
287:5 288:13,15

shown 34:14,20
38:11 51:2 52:2
53:3 54:13 55:10
56:10 57:13 60:7
61:18 63:11
64:21 65:4,19
66:5 83:10,22
86:7 89:15 90:7

118:5 142:8
146:6,9 148:18
166:11 167:2
169:11 184:12
186:22 187:1
192:7 196:8
197:11 201:19
238:16 259:1
261:4 274:12
313:11 320:10
326:15 332:3

shows 47:3 53:4
56:9 59:13 67:3
69:19 70:10
75:2,6 84:21
99:21 113:22
127:22 137:14
138:4 146:8
158:8 168:7
172:8 177:7
189:13
192:12,22 200:5
209:14 229:18
230:14 231:5
271:21 307:6
320:11 342:22

shut 116:21

Sick 13:16

sides 254:5 261:14

sign 87:15 315:16
337:16

signal 77:7
78:15,18 89:2
132:6 133:20
136:19 138:17
150:3 250:18,19
291:21,22
296:8,12 303:8
304:11 307:22
309:19 322:13
324:10
334:4,13,14
338:16

signals 68:13

130:17 291:2

signed 329:7

significance 44:18
56:8,12 57:4
63:18 65:11
77:10 84:3
165:20 171:10
179:21
189:16,22 190:8
193:8 194:1
195:2,6,11
206:14 209:8

significant 28:13
30:20 33:12
37:18 43:8 44:15
51:3 55:20
56:6,17 58:1
59:4 62:1 63:14
64:17,18 65:20
66:20 76:5 90:12
102:14 111:22
118:5 121:2
153:13 160:14
168:12,18 174:5
175:21
176:11,22
179:10 188:3
189:13
191:3,8,14
193:7,19 197:22
199:17 200:2
204:12 227:4
244:19 263:12
272:20,21
273:15,21 279:9
281:7,11 284:16
321:17 322:1

significantly 34:1

SIKES 348:2,12

silence 18:5

silly 242:18

Silver 1:17

similar 27:13
29:12 55:1 60:8

63:10 68:2
69:7,20 71:9
72:20 78:13
80:15 83:16
106:15 136:4
137:16 142:19
146:6 147:9
148:17 149:8
159:19 160:9
161:2,12,20
164:1 175:3,19
176:8 178:10
187:15 188:6
193:5 195:21
196:19 200:18
201:19
211:15,19,21
212:1,3 222:4
223:7 239:4

similarity 161:22

similarly 43:1 57:6

simple 109:22
125:5,14 127:1
183:20 234:6
237:8 261:2
320:5

simply 35:17
43:10 60:19 86:9
141:12 256:13
260:2

simultaneously
125:10

sing 247:9

singer 244:7

singing 242:18

single 30:13 59:4,9
100:15 157:4
161:1 171:6
219:10 254:1
318:5

sinuses 244:16

sir 100:10 143:7
147:14 210:10

sit 105:15

site 221:21

sites 157:5
159:11,14
216:11 272:15
306:14 307:1
311:16

sits 112:11,12

situation 69:14
215:11 260:6,20
335:1

situations 270:18
271:15 310:19

six 24:14 27:7
31:21 33:9
46:8,12 49:21
50:4,17
51:9,13,15
52:7,12,19,21
53:6,10 55:10
56:18 57:5,14
62:17,18,19 67:5
71:10,14,16
76:20,21 77:8,14
78:2,13,19 81:7
86:8,18 88:1
91:20 101:14
111:21 115:11
116:22 117:1,13
118:11
119:3,7,12,18
120:1,3,16
133:10 139:1
147:3,7 154:22
160:4 166:13,15
177:8,10,19
180:3 189:12
192:1,8 193:9
198:8 202:14
203:10 205:5
221:19 232:22
249:6,12 256:11
257:2,16 258:6
267:10 269:3,20
288:5,11,14,17

289:17 290:18 299:4 305:9 309:4 312:5 318:5 319:21 321:3 323:2 330:20 334:8 335:15,22 341:7

six-month 147:1 155:15

six-week 107:9,17 109:14 120:12 121:6

six-year-old 144:15

size 51:20 56:10 60:21 65:17 135:6 179:7 278:4 281:1,10 292:2,10 295:17 299:14 302:2 326:20 327:13

skewed 317:2 319:11

skip 91:6

slide 64:8 99:3 111:19 113:22 126:13 131:13,19 133:6 135:3 146:8 148:19 166:7 172:8 177:7 184:4 196:12 201:4 207:11 210:11 211:5 229:17 230:4,12 249:5 250:12 252:2 265:20 267:7 270:13 286:3 288:12 296:6 308:17 309:5 312:21 313:10,11 320:10 321:2,21 322:2 323:1,5 324:15,19

327:12

slides 48:11 51:21 125:12 133:8 173:17 201:16 211:19 220:8 293:4 297:8 317:13

slight 320:16

slightly 107:1 137:2 162:3 164:17 165:11 171:11 188:9 199:17 210:9 273:11 309:9

slope 82:11

slow 43:4 82:13

small 28:17,22 66:2 118:9,16 128:15 147:16 156:2 191:16,17 194:8 195:5,13 206:15 273:10 274:1 281:5 282:15,19 303:4 305:17 308:20 309:16

smaller 83:17 145:3 147:9,11,22 171:21 177:14 179:7 180:3 186:6

Smartphone 150:15

smears 35:9

solely 186:2 190:6 205:22 338:16

solid 141:19,20 142:1 184:13 185:3

solution 35:8 261:14

solutions 301:9

somebody 58:16 271:21 292:7

someone 58:14 276:10 318:1

someone's 216:12

Somerville 5:15 18:20

somewhat 30:10 181:11 186:5 226:9 262:12 293:6

somewhere 283:11

son 240:12

sorry 93:2 95:20 97:21 99:20 102:7 123:3 128:11 142:1 149:19,20 223:5 237:1 281:19 299:16 308:8 318:17 319:1,17 337:8

sort 95:1 121:17 136:20 146:13,14 151:3 225:3 227:22 280:10 282:21

sorts 278:12

sought 27:6

sound 262:20 281:9

sounds 245:11

source 151:5

sources 78:14

South 14:15 138:7 143:16 289:9 307:1,2 342:10

span 225:2

speak 22:5,13 130:22 134:15

214:2,14 219:4 229:8 234:14,22 264:2 277:20 291:17 303:16

speaker 212:22 214:6,9 218:1 220:5 222:5 224:8 229:2 232:22 234:19 239:22 244:3

speakers 212:14 214:6 235:9 248:12

speaking 24:8 32:22 213:13

speaks 294:9

special 23:3,16 71:21 173:19 180:17

specialist 245:5

specific 24:17 26:6 40:10 107:15 110:8 112:8,14 113:8 132:13 134:22 189:2 192:13 199:5 201:1 204:9 250:22 251:12 256:18 264:7,8,9 269:6 286:9,13 306:18

specifically 66:18 75:16 110:9 119:10 131:16 133:16 155:22 182:8 199:11 200:9 201:15 204:22 300:18 339:21

specification 167:6

specificity 119:18 123:18 249:9,16

250:20

specified 162:8
163:10 165:8
166:3,4 168:8
172:3,4
176:16,19 180:9

specify 162:9

speculate 232:10

speculation
312:17

spend 41:19
218:14 219:7
222:20 234:7,10
236:4 242:18
243:12

spending 225:14
234:8

spent 152:12 230:1
243:7 244:20
251:3

spills 116:15

spiral 217:12

spirit 22:7

spirometric
190:21

**spirometric-
driven** 101:21

spirometry 47:13
52:21 53:9 175:5

**spirometry-
related** 175:2

split 66:6 75:7
76:19 99:19
137:15 141:5
147:3 344:6

splitting 101:22

sponsor 13:4 14:4
32:4,15,22
125:5,12 126:4
130:16 153:15
154:15 155:12

156:8 157:1
191:19 195:9
203:12 204:1
208:7,13,20
213:3 248:22
274:4 275:13
287:21
291:3,6,17 292:7
298:17 299:10
313:5 331:22
332:2

sponsored 24:13

sponsors 345:20

sponsor's 32:11
156:10,19
189:8,15 190:4
192:5 213:5
343:11

spores 216:12

sports 240:13

spouses 24:3

spray-dried 35:9

Spring 1:17

spurious 102:4

sputter 115:16

sputum 48:8 61:17
62:6 64:22 67:9
69:4,9,14,15
74:9 82:19,20
120:10 303:12
324:1

stabilize 217:3
236:5,6

stable 247:2,13

staff 79:20

stage 131:9

stagnant 61:15

stand 264:15

standard 27:20
46:14 47:18
50:20 51:7 63:10

67:14 80:1 92:8
104:21 105:4
122:16 161:16
195:2 254:18
255:7 265:21
271:5 332:1
333:19 336:10
337:6,9 339:5

standards 263:22
278:11
333:3,9,12 334:1

standing 25:1

standpoint 226:21
252:3,4 261:8
332:8,20 346:4

stands 271:5 292:4

Staph 222:7
223:2,16

start 18:15,16 47:7
86:11 141:20
145:12 148:3
232:8 249:3
258:2,12 320:1
328:8,10 329:18
331:13 337:3
341:18

started 18:4
120:14 128:14
245:18 303:8

starting 47:4
105:19 144:7
268:8

starts 35:16 147:8
231:9

state 6:9 81:3
156:14 261:13
277:12
330:11,12
331:14 347:19

stated 90:13
207:19 209:1,5
279:1 314:5
339:14 341:21

342:13 343:17
345:6

statement 12:6
22:19 179:12
213:1,9,12
265:22 328:18

statements 25:2
331:2

states 27:21 37:14
43:20 46:6 65:9
219:11 233:9
252:22 307:2
329:4

statistical 11:12
15:11,13 21:5
36:12 44:18
50:22 56:8 63:18
65:11 84:3 122:9
153:5 156:9,17
162:9,18,19,22
163:11 164:22
165:2 167:22
169:22 170:6
171:10 175:21
178:11
179:10,21
180:14 181:17
188:17 189:22
190:8 193:7
194:1
195:2,6,11,17
206:14 209:7
258:20,22
320:11,22

statistically 30:14
63:14 64:17
135:15
168:12,17 174:4
176:10,21 188:3
189:13 191:8
253:15,21
254:2,11 259:11
272:8 273:15,21
321:17 342:8

statistician 122:13

126:10 162:21

statisticians
180:13,20

statistics 258:22
260:19 261:2
277:17

status 23:7 52:22
155:8,10 307:20

stay 216:19 260:15
275:9 286:21,22
288:17 304:10

stayed 90:8 260:7
296:21

step 119:15 261:3

stepmother 214:22

steps 282:15

stepson 215:2

stick 105:7

stickiness 39:4

Stone 4:6 19:19
333:17,18
339:3,4
343:15,16

Stony 6:18,19 19:1

stop 122:3 183:1
217:13 260:3

stopped 117:18
121:16 182:5
259:20 280:14

stopping 145:5,10
165:19 238:8

stopwatch 243:6

store 237:8

stories 215:22
343:12

story 112:12
118:20 188:6
215:22 280:22
281:1

straightforward

261:2

strains 162:4

strategies 39:20

strategy 87:6

stratified 161:17
164:3

street 224:11

stress 56:9 82:16
85:14 86:1 92:3
125:6 180:20
220:13 240:17

stresses 278:6

stretch 261:1

strict 274:22

striking 279:18
283:17 342:5

strong 183:2
227:22 253:21
254:11 258:21
333:16

stronger 149:14
217:12 287:21

strongly 21:22
232:13 277:20

struck 277:15,18

structure 39:15

structures 303:14

struggle 311:5

struggling 311:4

stuck 304:1

studied 45:16
65:18 66:1,16
84:12 98:12
161:13 266:18
275:14 301:16
328:1

studies
29:11,13,18
33:16 34:14,20
36:11 44:8,9,21

46:1,7,9,16 48:1
51:8 60:20
65:7,16 67:10,22
68:1,14 72:9
73:18 77:15 78:7
83:17 84:14
85:10,15 86:3
89:1 97:8 99:10
106:12,21
111:13 118:4,20
120:8 136:7
137:18 138:14
139:22 145:20
148:17 149:4
156:17,21
157:1,3 158:21
159:2,5,17,19
160:8,13,18
161:12,20
162:1,6 163:5,22
164:2,7,14,18
165:3,12
167:16,18 170:5
176:16 178:12
191:6 192:9
193:18 196:14
239:4 253:13,14
273:10 276:15
283:9,12 285:6
292:11 295:13
301:19 305:9
314:8 316:12,22
317:7
320:14,17,21
323:21 324:17
327:19 331:18
345:14

studying 253:14

study's 47:3

stuff 212:7 223:7
304:1

subgroup 44:6
65:13,17
66:3,9,16
134:14,17
153:17 163:20

177:2,5 189:3
200:8 201:2
203:9 205:8
228:6 230:9
271:22 272:1
320:4

subgroups 48:10
65:4,10,14,20
201:11 271:21

subject 23:5 73:6
154:9 169:5,8
170:4 172:7,14
173:21 174:15
327:5

subjective 279:22

subjects 34:22
55:6 63:2
68:6,7,8 71:3,17
73:16,20,21
77:22 114:14,16
122:21
164:10,13
165:15 167:4
169:12
177:14,19,20,21
178:16,19
181:20
192:19,22
196:18 198:22
202:12
203:16,21,22

subject's 75:8

Subjects 164:5

submission 343:11

submitted 189:9
207:13

subpopulation
28:18 33:18
134:19 252:14
283:18 290:4
291:14

subpopulations
198:16 284:21

290:2 335:18

subsequent 28:9
100:3

subsequently 46:1
109:6 163:9

subset 124:3,8
135:6 227:8,10
228:12,16
279:9,11 331:20
332:11

subspecified
269:21

substantial 31:7
182:3 188:8
191:14 207:13
252:5 253:1
255:14 256:21
257:13
270:3,13,17
271:5 330:18
333:4 341:5
342:15

substantially
187:21 204:10

subtherapeutic
46:2

subtracted 130:4

subtype 264:7

subtypes 264:11
271:18

succeed 241:22
242:17

success 275:20

successful 177:18

successfully 51:3

suddenly 303:12

suffer 183:16,22
216:5

suffered 246:18

suffering 233:10

suffers 82:9
182:20 326:8

suffice 253:19,22
254:3

sufficient 31:19
156:4 252:14
257:8 325:14
336:14 339:20
340:15

sugar 27:2

suggest 30:17
31:19 53:10
66:14 127:4
137:17,20
301:11 322:7
331:17

suggested 117:22
182:14 183:7
185:12 253:7
255:2 266:2
335:11

suggesting 31:10
63:18 193:1
195:19

suggestion 66:16
174:18 279:8

suggestions 118:7

suggests 45:22
119:6 127:5
137:12 144:21
168:20 169:18
171:20 178:5
179:6 193:3
195:20 203:13
309:16 331:19

suitable 155:21

suited 91:8 109:8

sum 67:3

summarize 80:19
179:9 189:7
204:7

summarized

113:14

summarizes 45:14
321:13

summarizing
163:15 172:5
323:2

summary 54:5
170:3 178:11
228:9 232:12
279:5

Sunshine 22:8

SUNY 6:18 19:1

super 219:18

superior 308:11

supervise 180:12

supervision
335:12

supplement 172:3

supply 221:11

support 45:13
51:11 55:20
63:16 66:21 69:1
79:19 149:11
156:4 185:22
188:5 189:15
191:5 195:8,12
205:20 206:15
209:6 256:9,16
257:8,13 258:4
294:20 312:18
322:17 333:4
336:14 341:5
343:11

supported 61:17
67:7 80:22
333:14
334:19,20

supporting 85:12
161:21 209:17
214:18 336:1

supportive 59:11
64:11,18 80:6

171:17 174:17
176:3 207:14
274:13 288:19

supports 43:22
45:17 51:1,13
87:6 190:4

supposed 343:1

supposedly 209:3

sure 97:3 99:13
106:8 109:19
117:10 124:13
127:9 131:1
149:22 210:1
229:9 267:5,19
299:18 312:15
329:11 331:16

surface 34:16 35:2
39:3 40:17
41:2,3

Surgery 215:9

surprised 147:15

surprising 59:4

surprisingly 64:6

surrogacy 323:4

surrogate 60:13
253:16 271:10
278:8,10 284:5
285:7,8
322:18,19 324:1
335:21

surrounding 79:8

survival 216:2
233:21 253:22
281:6

suspected 93:20

sustain 238:13

sustained 42:21
51:14 67:4

swallow 216:16

sweet 158:19

switch 146:10

switched 309:15

symptom 35:5
247:20

symptomatology
144:7

symptoms 28:19
40:2 153:18
199:18 247:22

system 197:12
216:9,16 237:7
258:15 276:20
329:16

systematically
185:4

systemic 238:2

_____

T

_____

table 12:1 13:1
14:1 15:1 16:1
17:1 18:15 56:8
59:13 65:19
69:19 70:10 75:2
153:20 162:5
166:11 167:15
168:7 173:20
175:11 189:18
197:8 198:4
200:5 249:13
261:21

tablet 150:15

tackle 88:22

tag 258:11

taking 31:8 58:7
93:13 96:18
116:4 171:2
172:15 182:5,7
183:1 199:19
221:21 236:5
238:4 246:16
259:20 260:3
290:6 303:7

322:5 337:15

talk 97:7 163:3
180:22 181:3
224:16 266:10
267:6 268:8,9
269:19 280:21
294:11,12
300:16

talked 230:7
235:17,18 326:3
328:2

talking 42:19
111:6 212:8
230:5,8 243:7
246:10 258:9
261:20
262:11,12
265:20 278:7
281:14 291:15
304:20 308:6
317:10
328:10,11

target 94:8

targeting
238:15,19

task 248:18

taste 158:19

TDN 146:21

teaching 24:8
215:17

team 10:13 175:7
188:17

teams 215:15

technical 128:21

technique 109:21
211:11

techniques 79:13

teenagers 137:19
138:18,19

teens 216:3

temporary 6:3 7:3

8:3 9:3,17
23:3,12,22 24:20
25:1,12 103:12

Ten 246:2,5

tend 132:8 259:15
286:21,22
288:17 315:6

tennis 244:7

term 59:20 60:1,15
66:21 70:12
91:16 108:12
150:20 185:19
209:4 305:8
338:12,17
344:15

terms 65:20
97:21,22 98:1
103:8 104:13
106:16 107:4
109:5 110:22
112:14 117:20
119:19 131:12
134:11
136:5,10,16,19
137:1 143:22
145:15 146:17
147:3,4,11,12
148:9 149:3
185:14 197:11
201:15,20 210:7
224:18,21
228:18
249:11,12,16
271:6 272:13
273:1 280:2
284:22 286:8
292:19,21
293:17 296:8
300:3,4,5,22
301:5,17
307:1,20,21
308:18
320:13,16
321:14
322:4,9,13

323:21 325:3,10
328:12

terrible 140:8

Terry 4:12 20:10
93:3,4,9,12 94:3
96:7 111:17,18
322:15,16
333:5,6 339:15
343:3,4

test 27:13 34:7
46:21 72:5,13,14
86:22 93:6,8,19
94:5,7,10
95:5,13 97:1
98:18 99:7
100:12
101:17,18
102:2,5,10
103:21 104:19
106:3,11 107:15
108:14 109:7,8
112:21 114:19
115:1,3,8 122:20
123:22 154:15
157:11,13
159:21 160:21
164:15,17
173:17 199:13
206:20 227:15
250:3 290:8

testament 142:11

tested 56:9 282:22

testimony 24:7
278:20 279:9,19
331:18 347:4,7

testing 47:2
100:22 105:22
160:22 272:22
278:11

tests 254:19,21

text 78:21 166:11
167:2,14

than/less 99:18

than-expected 44:16

thank 18:10 21:18 22:19 25:22 26:9 31:22 32:2,3 37:3 43:14,16 67:16,18 81:12,15 92:18,20,21 95:3 97:20 104:14,15 111:16 120:7 121:13 122:7 130:12,13 131:6 135:1 139:13 149:16,18 150:21 151:7,8 152:15,17 162:20 180:11 188:10,12 207:15,17 210:13 212:10 214:4,13 217:20,22 220:3,5 224:5,7 228:21 229:1,3 232:20,21 234:18,19,21 239:21,22 240:7 244:1,2,4 248:10,11,12 249:3 251:7,8 257:21 261:6 263:18 264:18 265:16 272:4,5 276:2 277:8 278:1 287:8,9 289:3,5,22 290:17 291:19 296:5 297:4,5 299:1,7 317:20 329:14 332:21 336:11 340:12 342:11 345:18,19,21 346:1,4,5

thanks 215:15

241:6 316:10

that's 48:14 94:16 98:16 101:11,12 103:16,19 106:4 112:7 116:17 117:2 125:7,20 128:9 129:3,20 134:3 137:12,20 139:1,11,17 140:16 142:9,17 145:11 181:11 186:12 187:3 211:7 218:19 224:9 246:4 260:3,4,14 265:15 267:13 269:10 277:4 279:2 280:16 289:6,8,14 290:17 291:3 293:18 294:20 295:2,15 300:15 304:8 310:9 311:10,11,13 317:5 322:11 323:12 330:8 341:1 344:8

theme 225:4

themselves 25:17 108:8 110:12 150:14 156:4 304:13

theories 304:14

therapeutic 66:2

therapies 28:19 39:20 41:19,20 43:7,9 82:22 85:11 86:9 88:18,19,20,21 90:5,20 91:5,14 161:16 219:8 221:8 223:19 234:3,8,10,15 236:9 237:5,17 238:2,7,9 241:7

258:19 265:2 282:8 314:16

therapy 38:1,15,21 40:18 41:2,11,17,21 43:11 46:14,15 70:9 79:19 82:12 86:15 90:8,15 91:12 104:7 118:5 153:17 218:13 220:22 221:5 224:19 226:19 237:10,15,20 238:12,15 244:22 261:15 262:2 263:17 274:22 275:10,14,21 279:18 286:11 287:4 294:14,20 295:1 335:15

thereafter 347:5

therefore 35:1 38:20 43:11 46:20 48:18,20 50:1 51:20 52:4 56:2 57:15 59:16 64:5 69:13 126:20 127:1 141:11 147:10 169:5 170:20 190:14 206:14 214:2 298:3 300:8 307:19 344:6

There's 112:17 272:21

they're 135:7,8 140:4 271:19 310:2 311:11

they've 147:9

thick 35:4 216:18 244:20 245:10

303:13

third 42:3 148:7 256:15

thirdly 326:7

Thirteen 62:13

thirties 215:3

Thomas 1:19 11:5 16:7 153:6 347:2,18

thoughts 108:21 268:20 269:8 270:7 281:16 299:1 336:17

thousand 327:15

thousands 248:8 255:22

threatening 260:21

three-to-two 46:10 160:3

threshold 58:10 103:8 105:3,12 172:18,21 173:13 174:8,16 177:16

thresholds 59:9 173:8,19 192:13,20

throat 5:13 204:17

throughout 46:16 47:2 74:16 103:14 113:13 114:13 115:12 153:1 167:10 229:13 237:21 245:22 247:11 308:22

throw 217:9 258:11

throws 305:6

thus 22:4 40:10,22

42:21 161:6

tie 108:2

tighter 275:1

tilt 35:21

time-consuming
40:22 42:3 236:8

time-efficient
248:5

timeframe 191:14

tipping 56:4,19
57:1,3 83:22
129:2,12 130:5,8
278:12

tips 109:22

titles 240:18

tobramycin 50:10
84:17,20 85:17
301:8 314:9,19
325:5

toby 303:7 317:9

today 26:11,19
27:6 30:1 36:18
37:20 80:18
81:16 154:8
163:2 165:13
179:16 213:20
214:14
215:16,21
217:20 218:19
220:3,10,13
224:15 229:8,18
230:22 231:13
235:1,9 240:9,20
241:6,9 242:10
243:19 248:13
254:5 261:20
268:5 321:21

today's 21:21
22:1,21 23:11,21
24:10 26:12
154:9

tolerability 36:20

40:21 41:13 60:2
70:8 74:1 79:14
81:5 86:16 90:4
101:18 104:21
109:6 115:13
116:14 122:10
199:2,10 202:16
204:15 206:22
227:7 249:12
252:11 340:8

**tolerability-
related** 90:3

tolerance 46:21
72:5 86:22
93:6,8 94:5,6,10
97:1 106:11
107:15 109:7
114:19 115:1,8
157:11 159:21
164:15 206:20
227:15 237:16
250:2 290:8

tolerate 59:16
86:7,10 105:2
107:18,21
108:12 111:11
116:8,10 122:21
161:1
182:4,13,22
194:13 206:11
223:20 239:18
290:11

tolerated 107:17
183:13 206:18

tolerates 182:8

tolerating 119:22
226:13 227:10
239:7

tolerators 116:6
123:6 182:17
194:12,21
206:10 290:5,10
332:2

Tom 21:7 180:12

Tony 21:12

tool 217:5

top 35:17 67:14
118:5 129:13
141:21 145:21
184:15 185:3
249:13 250:10
273:16

topic 22:10,17
31:4 107:7 252:1

topics 21:20 44:12
155:12 213:19

Toronto 13:15

total 34:11 35:12
68:10 76:14
95:12 133:12
160:17 161:1
198:7 202:8
316:17

totaled 49:7 62:10

totality 92:4
256:20 296:10
321:19 330:17

totally 263:15

totals 197:11

touch 268:21
270:3

touches 215:18

toward 291:13

towards 173:9
303:17,18

toxic 300:12

toxicity 182:20
262:3 294:13
295:1 300:17,22
301:3

toxicology 302:10

track 120:4
289:16,18,21

tracked 146:2

314:10

tract 69:13 198:2

Tracy 9:5 20:18
139:12,13
277:9,10 302:6,7
304:3 310:18
332:5,6
340:13,14
341:22 342:1

trade 24:12
154:12,15 234:1

training 21:11
152:11

trajectory 289:11

transcript 348:4,6

transcription
347:6 348:1,7

Transcriptionist
348:12

transient 72:19
293:15 296:20

Translational 11:9
15:16 16:10 20:2

transmembrane
28:6

transparency
24:22 32:7
212:17

transparent 32:5
212:16

transplant
233:17,22

transplantation
233:22

transport
221:13,15

transportability
34:17

travel 32:14 81:17
129:7 213:5

treat 26:14 28:19 36:19 49:6 62:9 85:2,12 88:15 92:17 153:17,18 183:16 199:14 210:18 227:16,17 228:15 247:22 273:6 318:14 334:18

treated 41:6 58:17 83:16 92:8 96:13 100:12 181:2 182:19 187:12 200:14 201:6 202:1,4 204:13 207:3 210:5 213:22 297:15 307:7 321:22

treating 40:2 42:17 74:5 92:11 271:7

treatment 29:3,16 30:4,9,17 31:3,13 34:3 36:10 37:8,19 40:11,13 41:13,15,16 42:9 43:8 52:20,22 54:4,13,21 57:17 59:22 60:1,3,5,19 63:14,22 66:15 69:7,15,20 72:16,17 73:5 74:7,21,22 78:12 79:5 83:13,17 84:6,11,13,19,21 85:8,10,13 86:11 90:9,13,16 91:3,7,9,10 92:1 102:12 104:22 106:16 107:11 113:5 115:10 120:15,18,22 121:2,17 122:22

124:5,19 125:2 157:15,22 158:4,6,10,13 163:7 164:6,21 166:19 167:10,13,17 168:5,9,17,20,21 169:9,10,17,21 170:7,21 171:12,20 172:14 173:11,18 174:5,15 175:2,10,22 176:4,11,18,22 177:17,18 178:1,9,17,20 179:4,7,11 180:1,5 182:4,14,22 183:8,14 184:14 185:18 193:9 194:7,11,16,21 197:17 198:10,22 199:16,18 200:12,16,19,21 203:17,20 204:21 205:2,6 206:7,12 219:6 221:7 222:9,14 229:10,15,16,21 232:5,15 234:16 236:20 241:4 242:12 243:3,15,17 245:17 246:4,17 247:4 264:9 272:22 273:2,12 274:8 278:6 281:3 294:13 295:17 298:4 318:7 336:13 340:3 343:14 344:2

treatment-related

178:13

treatments 40:3 41:1 42:12 118:1 153:21 215:20 217:5 218:11,19 219:8 220:18 229:13 230:1,3 235:10 236:17 243:9,13 246:20 328:5

treats 247:19 248:2 254:6

trend 61:11 66:4 176:4 209:13

trends 61:9 64:10,18 174:7,10 176:3 191:7

trial 29:10 74:16 78:11 87:4 89:13 97:17 101:7 109:9 111:4 114:9 117:5 140:10 145:6 209:17 226:8 245:7,14 254:9,11 260:7 272:9,19 280:14 284:17 287:4 295:10 303:18 307:16,17,18 316:4,22 324:17 334:2,4,12,13

trials 29:11 31:2 33:13 46:3 54:4 65:13 78:8 81:16,21 83:11 84:18 85:17,20 86:22 87:21,22 98:13 101:2 106:7 132:11,17 152:19 156:22 159:1 198:9 230:6,7 269:14 270:17

271:14,19 272:7 284:13,20 295:12 299:21 312:1 335:17

tricky 270:4

tried 61:1

trigger 109:16

trip 236:15

trouble 183:9 233:17

trough 103:16

true 30:5 52:6 63:16 76:2 128:9 140:3 168:4 260:3 266:12 282:6 347:6 348:6

truly 191:15

try 41:8 101:22 122:10 125:6 132:16 143:13 150:18 184:9 221:12 222:1 235:12 241:19 267:5 276:12 285:18 286:6 313:19

trying 93:22 107:20 109:1 140:5 194:10 217:7 228:1 255:12 268:18 286:2 287:16 290:4 294:21 311:10

t-test 181:15

turn 32:1 37:1 43:14 81:12 162:15 180:16 248:17 317:15 337:7

TV 242:20

twenties 161:14
314:3

Twenty-nine
49:15

twice 27:9 29:7
44:22 45:3
47:11,17 50:14
102:18 108:4
155:1,3
157:16,19 158:5
196:7 198:10
201:22 203:7
204:12,20 207:1
246:3 256:10
257:1,15 258:5
330:19 341:6

twist 35:17

twitchy 103:21

two-sided 165:20

two-week 29:3
45:1 157:17

type 69:21 124:9
165:19 166:3
180:4 209:13
211:15 228:5
254:15 261:15
284:15 285:1
306:6 311:16

typed 348:4

typewriting 347:5

typical 82:10
90:18

typically 84:4,7
87:14 88:2,14
156:16 194:19
253:11

_____
U
_____

U.S 13:9 28:13
33:3 34:6 37:20
63:8 65:3,4
138:5 159:15
229:22 248:9

273:13,20
292:15 328:5

U.S.C 23:15

UK 111:5

ultimately 28:15
39:15 116:4
286:17

Uluer 234:21
235:2 239:22

UMDNJ 5:10

unable 182:3
206:19

unacceptably 38:3

unbalanced
51:16,19

unblinding 165:5

uncertain 33:18

uncertainty 79:8
125:13,16 126:3
128:10
129:9,10,14
187:16,18

unchanged 46:15
69:14

uncommon 304:22

uncontrolled
86:13 146:14

underestimate
313:22

underestimated
171:7 305:2

underlying 170:17
248:2

underneath 142:1

underpowered
117:19 327:19

understand 32:8
101:22 115:7
212:19
242:12,13

251:22 252:19
275:3,15 291:9
294:21 295:5
339:20 340:16

understanding
167:8 170:10
180:15 249:11
291:13 340:9

understood 97:3,6
210:1 289:4

undertake 60:20

undertaken 72:5

underwhelming
276:3

unequivocally
319:14

unexpected 161:12

unfortunate 345:7

unfortunately
91:5 183:4,15
250:12 307:12
316:3,5,8

unique 259:13
310:19

unit 232:6

United 27:21
37:14 43:20 46:6
65:9 159:12
233:9 307:2
329:4

universal 54:7

universally 284:6

University 2:20
3:9 4:15 5:10
6:9,15 7:9,16 8:9
9:7,14 13:15
14:15
19:11,14,17
20:6,14,19,22
229:7 240:11

unknown 177:22

unlike 54:19 86:2

unlikely 120:3
126:19

unloads 82:20

unmeasured
124:15

unmet 13:12 36:9
37:2 224:2
235:16 287:17
333:2 334:12
344:7

unplugging 60:11

unrealistic 84:3

unrealistically
184:22

unrelated 254:3

unrestricted 240:5

unsafe 254:22

unsure 330:1

untaken 170:9

untimely 39:16

unusual 312:2

updated 91:14

upon 30:1 48:15
50:3 53:14 66:7
191:3 263:11
314:1 316:11
332:17 340:7

upstream 83:1

urgent 224:1

usage 154:1
275:20

USC 23:10 24:4

useful 54:1 60:12
67:11,13 97:10
113:7 122:15
123:20,21
131:2,4 135:19
139:11 141:16
142:17 148:10

186:19 249:10 306:21 310:10 321:2

usefully 147:1

user 65:13

users 62:6 118:12

usher 241:7

usual 195:2

usually 60:17 74:12 180:20 276:5 295:9,13,14 297:1 315:16

Utah 229:7

utility 36:21 119:16 286:8 287:1 334:15

utilize 159:1

utilized 166:10 169:3

utilizing 167:3 168:1 189:9

_____ V _____

V0 141:1

V1 140:22

vague 294:9

valid 53:15 124:21 284:7 289:14

valuable 282:1,4

value 51:5 55:9 58:13 126:14 128:15 142:4,5,15,16 171:6 195:3 242:14 260:8 273:11 274:1 280:22 325:1

values 30:18 58:8 62:2 143:2 186:6 187:16

250:13,14

variability 66:13 67:1 99:7 118:9 136:14 185:2,14 195:18 282:20

variable 48:1 58:7,9,19 60:14,18 155:22 308:18

variables 48:4 60:7 146:22 211:15 236:13

variance 128:16 129:16 171:7

variation 178:4

varied 313:14

varies 40:21

variety 21:21 122:18 125:6 155:20 213:19 241:19 284:9

various 167:5 184:5 192:20 283:4,12

vary 106:6 185:5

vast 216:5 292:15

Vegas-style 291:9

ventilation 61:15

veracity 309:18

verifies 279:22

versus 70:21 99:11 107:12 121:3 130:22 133:4,19 134:2,3 135:20 140:22 143:9 149:11 194:16 197:19 198:3 199:1 202:4,15 204:6,21 205:7 232:2 234:8 293:19 295:6,9

296:11 297:16 299:12 300:19 321:22

vertical 172:19 187:6 192:15 211:7

vest 220:22 283:5

vice 33:3

vicious 39:13 82:3 83:2

view 59:6 104:20 212:3 215:5 292:4,21 327:17

viewed 141:9

views 22:3 346:5

vigorous 316:6

virgin 283:2

virtually 104:2 142:3 312:9

viscosity 35:3

viscous 35:4

visit 47:4 51:13 55:6 56:1,11 63:22 69:6 113:14,19 114:3 142:9 151:2,4 157:12 160:1,2,20 161:6 182:9,10 184:7 185:3,4

visited 306:22

visits 48:15 64:1 113:12 185:5

visually 135:13

vital 48:5 60:7 64:12 67:8

vitamins 218:12

volume 56:19 144:18

volunteer 233:4

244:8

vomiting 70:6 201:10 204:18

vote 207:22 208:2 256:3,20 269:8 280:3 329:17,20 330:1,2,3,4,5,9,1 2 331:7 333:14 336:17,19 340:6 341:2,13 344:6,7 345:9

voted 330:7,11,13 331:10,15,16 332:6 333:1,6,8,11,18, 22 334:11,17 335:4,20 336:2,6 337:5,9,11,22 338:7,15,21 339:4,8,13,15,19 340:14,20 341:15,20 342:1,4,13,14 343:4,5,6,7,9,16, 19 344:1,5,11,21 345:1,11,12

votes 329:20

voting 2:10 6:3 23:13 25:1,7,13 251:21 256:7,19 328:17 329:15,16 330:16 332:15 341:3

Voting)(cont 3:4 4:4 7:3 8:3 9:3

VP 13:9

vulnerable 277:1

_____ W _____

Wagener 9:12 19:10 99:2,3 112:16,17 114:6 211:9,10,22

258:10,11 262:8 281:19,20 304:15,16 309:20 319:22 320:1 334:16,17 338:6,7 344:10,11

wait 138:3

waivers 23:16 24:20

walk 49:8 95:1 135:22 141:17

warning 73:9 154:18

warnings 78:22 267:21

warrants 315:11,12,17

washout 157:17

washouts 157:20

wasn't 59:5 100:9 106:8 246:21 249:8 250:12 272:16 273:18,21 290:16 301:20 316:5 324:7

watch 219:1 241:12 242:20

watched 340:18

water 34:15 110:1 245:9

ways 54:17 113:6 115:14 125:6 128:13 144:12 226:22 227:5,21 229:10 243:5 259:10 283:4 295:8 323:14 334:20

weak 188:5 278:4,10

weapons 228:2

wear 240:18

weather 236:14

we'd 306:3

wedding 215:3

Wednesday 1:11

week 29:14 49:21 50:4 51:13 52:12,21 53:6,10 55:10 56:18 57:5,9,14,20 58:20 59:5 62:17,18,19 63:20 64:8 117:14 118:8,11 119:3,4,7,12,13, 18 120:1,3 140:22 164:15,21 166:13 174:1 176:20 189:12 243:11 247:10 249:6,7,12 288:11,14

weeks 47:11,13,15 48:16 52:7,19 55:15 56:3 61:21 68:12 78:11 90:9 111:21 113:15 115:11 116:5,22 117:1,13 118:14 120:16 145:7 157:20,22 159:5,18 160:4 164:6,15 245:20 284:15 288:5,17 312:5 335:15

weigh 89:18 232:2 295:6

weighing 304:11

weight 48:8 61:17 62:6 64:22 67:9 144:16 254:14

324:1,3 339:20

welcome 26:9 236:20 238:21

well-controlled 254:9

well-designed 253:12

well-focused 207:18

we're 137:20 141:21 212:12 261:19 262:11,12 270:5 316:16 324:10

we've 136:2,3,5,7 139:2 180:22 183:20 263:5 275:13

whatever 140:3 272:15 282:13 283:5 313:21

wheezing 223:19

whereas 108:6 151:2

Whereupon 346:7

wherever 223:9

whether 52:9 99:16 110:6 112:21 117:2,21 118:17 119:19 120:21 121:16 123:22 133:2 136:17 137:4,5 142:4 167:6 177:22 207:12 209:7 249:11,20 252:9 254:20 255:6 259:9 268:9 272:12 280:20 281:14 283:4 292:3 298:9 299:13 309:3 311:15,22

321:6 327:18

white 1:14,15 26:9 220:19 246:2

whole 54:18,21 57:17,19 59:6 115:12 185:22 193:6 207:6 225:16 273:22 280:16,22 281:1

whom 159:13,15 183:10 347:2

widely 48:1 58:8

wider 284:9

widespread 50:20

wife 241:12 242:21 244:7

willing 101:19 172:15 227:3 260:22 311:14

willingly 43:12

win 295:2

window 295:2

winning 253:15

Winthrop 6:15

wish 120:22 220:13 330:2 344:1 345:12

withdraw 53:2 197:6

withdrawal 44:16 50:8,11,12 51:16,19 52:19 53:5 59:2 63:1,2 64:3 110:3,5 111:13,20 112:15 167:20 169:18,19 179:1 197:5 200:7 205:9

withdrawals 56:1 57:7 90:3 166:19

188:22 204:20 206:22

withdrawing 52:6,12 53:11 57:5 62:18 63:3 101:16 193:21 310:6

withdrawn 50:6 62:21 101:20

withdrew 49:16,21 55:6 57:14 62:13,17 71:18 77:22 78:6 89:13 112:2,3 166:16,18 198:9,22

withhold 88:18

withholding 79:7

witness 24:7

Witzmann 10:16 15:7 16:14 21:9 152:8,9 153:12 162:20 188:12 297:4,5 315:21,22 316:10

woman 223:13,15

Women's 8:17 19:8 235:4

wonder 108:10 303:14,21

wondered 117:6 126:4 272:18 296:7

wonderful 223:13

wondering 94:4 107:14 125:22 143:8 280:20 300:15 311:22

woods 115:9

wording 338:1

work 40:1,3 43:9 90:21 91:3 140:5 215:5 221:12 241:17 242:17 269:9 270:22

working 40:4 152:12 221:9 235:6 236:3 251:3

works 35:15 40:6 222:17 241:16 258:15 259:5 272:1 280:1

world 219:4 230:8 232:18 235:21,22 306:17 309:1 342:10

worry 305:18

worse 122:2 128:4,14 282:15 326:10

worsening 52:9 53:11 66:13 112:11 126:19 127:4

worst 97:4,17

worst-looking 96:22

worth 242:14

worthwhile 331:18

writing 24:8

written 213:1 328:1

— X —

X-axis 172:17 192:12 231:6

xylosoxidans 223:2

— Y —

Y-axis 45:15 51:2 136:3 172:19 192:15 231:5

year-olds 133:11

yellow 220:17 230:2

yeses 331:11 336:22 341:16

yesterday 255:21

yet 41:14 57:22 82:22 84:19 107:3 144:5 265:12 274:10 324:9 331:22 332:13 337:15

York 6:19

you'll 31:13 145:22

young 82:9 92:14 120:21 144:12 150:5 229:12 234:14

younger 63:5 67:2 77:9 89:3 92:11 147:22 177:14 203:15,16,21 301:12

youngest 203:12 205:5 231:7

yourself 186:17,18

yourselves 212:9

you've 102:20 128:20 184:20 270:5

— Z —

Zealand 138:7 159:12

zero 115:11 119:20 140:21

168:22 177:19 186:5 192:7 205:7 320:3 331:12 337:1 341:16,17

Zhou 11:11 15:12 21:5 153:5 156:17 162:12,16,20,21 183:21 185:17 186:12 192:7 195:17 209:22 211:18 212:3 272:21 279:1 326:17,18

Zhou's 194:5

Zuckerman 245:6